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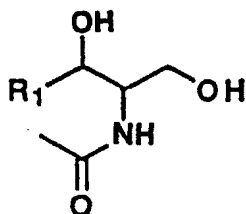
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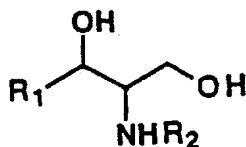
(54) **A lipid composition containing liquid crystal phase**

(57) The composition comprises a 2-acetaminoalkane-1, 3-diol or its optical isomer having the formula:



tive, a fatty acid and a derivative thereof. This composition forms a lamellar liquid crystal phase which can retain moisture. When the composition is applied to a human skin or scalp, it prevents the skin and scalp from drying-out or deterioration. The composition can thus be used as a cosmetic or pharmaceutical product.

in which R1 signifies a linear alkyl group having 9 to 17 carbon atoms;  
a 2-acylaminoalkane-1, 3-diol or its optical isomer having the formula:



in which R1 has the same meaning as mentioned above and R2 signifies a linear acyl group having 14 to 24 carbon atoms;  
as well as cholesterol, and optionally a compound chosen from the group consisting of a cholesterol deriva-

EP 0 875 232 A1

## Description

The present invention relates to a novel composition containing a liquid crystal phase, in particular a liquid composition comprising a mixture of compounds belonging to the ceramide family and a medium suited for cosmetic or pharmaceutical use.

The lipid composition according to the invention may comprise a racemic 2-acetaminoalkane-1,3-diol, i.e. N-acylsphinganine, or an optically active form thereof; a racemic 2-acylaminoalkane-1,3-diol or an optically active form thereof; and cholesterol, and optionally a cholesterol ester, e.g. cholesteryl hydroxystearate; iso-stearic acid; and / or other higher fatty acids.

The composition may further comprise a triglyceride, a phospholipid or other cosmetically or pharmaceutically acceptable vehicles or excipients. Such a composition may especially be appropriate for use as a cosmetic product, an externally applicable skin preserver, a bath additive, a hair-care product, or the like.

The composition described above is capable of retaining moisture on the subject to which it is applied. When it is applied on the skin, it renders skin humid and fair, and reactivates skin cells. The composition thus protects skin and provides a suitable cosmetic, dermatological or bath-additive product. When applied to scalp or hair portion, subsequent hair-washing does not cause a loss of water-soluble proteins or amino acids from hair, so that the hair is protected from drying-out.

To render the skin moist and smooth, the water content retained in stratum corneum (horny layer) of the skin plays an important role. Water seems to be retained in this stratum corneum by free amino acids, organic acids, urea, inorganic ions or the like, contained therein. Such substances are actually used alone or in combination for preparing a dermatological cosmetic product or medicine for external application, in order to prevent or cure a rough skin.

It has been found only recently that intercellular lipids contained in the stratum corneum have a high water-retaining capacity and usually contain about 30 % of water. These lipids control the evaporation of corporal water and prevent external stimulants from penetrating, thereby preserving a tender and smooth skin.

Amongst the intercellular lipid components, a ceramide in particular, but also a cholesterol ester, are known to improve rough skin, when applied thereto. Especially, the ceramide serves as an efficient barrier to a water migration.

The intercellular lipids consist mainly of ceramides, cholesteryl sodium sulphate, palmitic acid and cholesterol. In view of the above, a composition containing these same components, in which the ceramide corresponds to a racemate having formula (II), was prepared and described in Japanese Unexamined Patent Application under the number Hei 4-327 563.

Conversely, it was found that the level of ceramide content with a patient suffering rough or dry skin, or atopic dermatitis is considerably low as compared with the skin of a healthy person.

Ceramides were also isolated and identified by G. HUSSLER et al. from the lipids contained in human hair (Int. J. Cosmet. Sci., 17, 197, 1995). These ceramides have a high capacity for retaining water. A racemic ceramide was then synthesized and incorporated into a lipid composition for hair-washing. It was then argued that the lipid composition has the effect of reducing the loss of proteins and amino acids from hair when it is washed, so that the hair is prevented from drying-out and protected (European Patent 0 278 505).

It is also reported by M. PHILIPPE et al. that a composition containing a synthesized racemic ceramide has an effect of reducing the water loss of hair (Int. J. Cosmet. Sci., 17, 133, 1995).

Under these circumstances, research is currently being carried out into the application of ceramide-containing, intercellular lipid-type substances to the rough skin, in view of improving the state of the skin.

Ceramides are scarcely soluble in water or any organic solvent. To provide it in the skin, it is thus necessary to first prepare a lipid composition having a specific mixture ratio so as to form a lamellar liquid crystal structure and to put this intact structure into a cosmetically or pharmaceutically usable form. The lamellar liquid crystal structure can be formed when prescribing, by adding a fatty acid or cholesterol to the ceramides. The ceramides can be dissolved in a fatty acid, then incorporated into the lamellar liquid crystal structure. To the above purpose, a surfactant is usually added to promote the penetration of the lamellar liquid crystal structure into the skin, but any kind of crystal other than the ceramides should not be added thereto. Moreover, a specific sort of surfactant has to be chosen in order to promote the penetration of intercellular lipids into the stratum corneum and also to promote the formation of a lamellar liquid crystal. The intercellular lipids consist mainly of a ceramide, cholesterol, a fatty acid such as palmitic acid and cholesterol sulphate. A mixture of these components usually forms a lamellar liquid crystal structure. This structure can also be formed in the absence of the fatty acid or cholesterol sulphate. However, according to the report by P.W. WERTZ et al., the ceramide alone, or together with cholesterol, does not form a homogeneous lamellar liquid crystal structure (J. Invest. Dermatol., 87, 582, 1986).

On the other hand, there is proposed a hair-protecting composition consisting of a ceramide or glucoceramide, a cholesterol ester and a cosmetically acceptable vehicle (Japanese Unexamined Patent Application Sho 63-270 617). The ceramide or the glucoceramide, e. g. cerebroside used in this composition is extracted from a material of animal origin such as a pig skin, a bovine brain and a red corpuscle (haematid), or from a plant. Amongst these possibilities,

extracts from the bovine brain is considered to be the most appropriate product. However, since the eruption of bovine spongiform encephalitis (mad cow disease), this product might not be used any more as before.

There is also proposed a hair-protecting composition containing either a ceramide or glycosceramide and at least one kind of cholesterol ester (Japanese Patent 2 510 235).

5 In another study, a lipid component was chosen from the group consisting of a ceramide, a pseudoceramide, a polyester consisting of a polyol and a fatty acid, a phospholipid, a galactosyldiacylglycerol, a sphingoglycolipid, a derivative of succinic acid and a mixture thereof and provided into a lipid lamella, in order to cure xeroderma (Japanese Unexamined Patent Application Hei 6-157 283).

10 Further there was provided a composition for use as a bath additive containing a ceramide and a compound having a pseudo-ceramide structure (Japanese Unexamined Patent Application Hei 8-34 726).

Still further, there was prepared a mixture containing a complex product or composition having a liquid crystal phase, an amphoteric and/or semi-polar surfactant, a higher fatty acid and water. Use of the mixture enabled to conserve cosmetic make-up properly and longer, and to resist more efficiently the deteriorating effect of water and cutaneous fat (Japanese Unexamined Patent Application Hei 8-217 633).

15 It is therefore an object of the present invention to provide a composition which enhances the moisture-retaining capacity of the stratum corneum and cures a rough skin.

Another object of the invention is to provide a cosmetic or pharmaceutical product comprising this composition. The product cares for and protects the skin. It can be used as an externally applicable skin-care product.

20 Due to its moisture-retaining capacity, the composition also protects the hair from drying-out and splitting. A further object of the invention is therefore to provide a hair-care product.

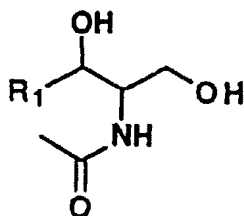
Still another object is to provide a composition or a product for use as a bath additive.

To this end, there is provided a composition comprising :

- at least a component A chosen from the group consisting of 2-acetaminoalkane-1,3-diols having the formula (I):

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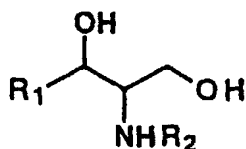
(I)

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in which R1 signifies a linear alkyl group having 9 to 17 carbon atoms; and an optically active form thereof;

- at least a component B chosen from the group consisting of 2-acylaminoalkane-1,3-diols having the formula (II):

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(II)

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in which R1 has the same meaning as mentioned above and R2 signifies a linear acyl group having 14 to 24 carbon atoms; a derivative thereof where at least one of said carbon atoms in the acyl group has a substituting group, and/or a double bond; and an optically active form of either of said diol or derivative; and

- at least a component C consisting of sterol group,

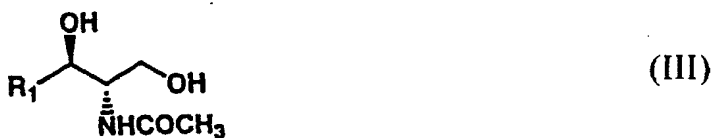
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said components A, B and C being mixed in such a proportion as to form a liquid crystal phase. The sterol may be cholesterol.

Preferably, the components A and B are mixed in a weight proportion ranging from 1 : 1 to 1 : 8.

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In a preferred embodiment, the component A is a (2S, 3R)-2-acetaminoalkane-1, 3-diol having formula (III):



10 where R1 indicates a linear alkyl group having 9 to 17 carbon atoms.

Likewise, the component B is preferably a (2S, 3R)-2-acylaminoalkane-1, 3-diol having formula (IV):



20 in which R1 has the same meaning as mentioned above and R2 signifies a linear acyl group having 14 to 24 carbon atoms; a derivative thereof where at least one of said carbon atoms in the acyl group has a substituting group, and/or a double bond.

R2 in the component B may be an acyl group having a hydroxy group on the position of carbon-2 or may be oleoyl group.

In the case that R2 is oleoyl group, the weight proportion of the components A to B, the components B to C and the components A to C ranges respectively from 1 : 1 to 1 : 8, from 7 : 1 to 1 : 1 and from 1 : 1 to 1 : 3.

The composition according to the invention may further comprise at least a component D chosen from the group consisting of a derivative cholesterol, a fatty acid and a derivative of a fatty acid.

The derivative of cholesterol as of component D may be cholesteryl hydroxystearate.

Then, preferably the total of the components A and B, and the cholesterol as of component C are mixed in a weight proportion ranging from 5 : 4 to 5 : 1, whilst the component C and the cholesteryl hydroxystearate as of component D, in a weight proportion ranging from 4 : 1 to 1 : 5.

Alternatively, the fatty acid or a derivative thereof as component D may be isostearic acid or cholesteryl hydroxystearate.

In the case of isostearic acid, the total of the components A and B, and the cholesterol as of component C are mixed in a weight proportion ranging from 5 : 1 to 3 : 1, whilst the component C and the isostearic acid as of component D in a weight proportion ranging from 1 : 1 to 1 : 4.

The composition according to the invention may further comprise at least one compound chosen from the group consisting of a triglyceride and a phospholipid.

The invention also provides a cosmetic product comprising the composition defined above and a cosmetically allowable medium.

The cosmetic product thus obtained may be used as a skin-protecting agent, an agent to be added in bath, a hair-protecting agent, or the like.

The invention further provides a pharmaceutical product comprising the composition defined above and a pharmaceutically allowable medium.

The composition may be used in the manufacture of a medicine for protecting skin.

To form a lamellar liquid crystal structure, the composition of the invention may be homogeneously mixed, heated above the melting temperature and then gradually cooled.

The composition may also be homogeneously mixed, supplemented with water and repeatedly frozen and thawed, so as to increase the hydration level.

Further, the composition may be homogeneously mixed, dissolved in a solvent and supplemented with water, so that a liquid crystal phase is precipitated out.

Moreover, the liquid crystal phase can also be formed by other methods.

The composition according to the invention includes all the products that contain the liquid crystal phase, notwithstanding these liquid-crystal forming methods.

The above and other objects, features and advantages of the invention will be made apparent from the following description of the preferred embodiments, given as a non-limiting example, with reference to the accompanying draw-

ings, in which:

Fig. 1 shows the reaction scheme for preparing optically active 2-acetaminoalkane-1, 3-diols from an ester of 2-acetamino-3-oxoalkanoic acid;

Fig. 2 shows a ternary phase equilibrium diagram consisting of a (2S, 3R)-2-acetaminoalkane-1, 3-diol (A), (2S, 3R)-2-acylaminoalkane-1, 3-diol (B) and cholesterol (C);

Fig. 3 shows a ternary phase equilibrium diagram consisting of a (2S, 3R)-2-acetaminoalkane-1, 3-diol and a (2S, 3R)-2-acylaminoalkane-1, 3-diol (A + B), cholesterol (C) and cholesteryl hydroxystearate (D);

Fig. 4 shows a ternary phase equilibrium diagram consisting of a 2-acetaminoalkane-1, 3-diol and a 2-acylaminoalkane-1, 3-diol (A + B), cholesterol (C) and isostearic acid (D);

Fig. 5 shows a ternary phase equilibrium diagram consisting of a (2S, 3R)-2-acetaminoalkane-1, 3-diol and a (2S, 3R)-2-acylaminoalkane-1, 3-diol (A + B), cholesterol (C) and isostearic acid (D);

Fig. 6 shows a ternary phase equilibrium diagram consisting of a 2-acetaminoalkane-1, 3-diol and a 2-acylaminoalkane-1, 3-diol (A + B), cholesterol (C) and cholesteryl hydroxystearate (D).

Figs. 7 to 9 show the results of a water-retention test effected with the compositions 1, 22 and 13 according to the invention, with respect to the corresponding blank samples;

Fig. 10 shows the comparison of water-loss rate between a racemate and an optical isomer thereof, effected with compositions 26 and 27;

Fig. 11 shows the comparison of rate of water loss between a racemate, an optical isomer and a pseudoceramide, effected with compositions 30 to 33; and,

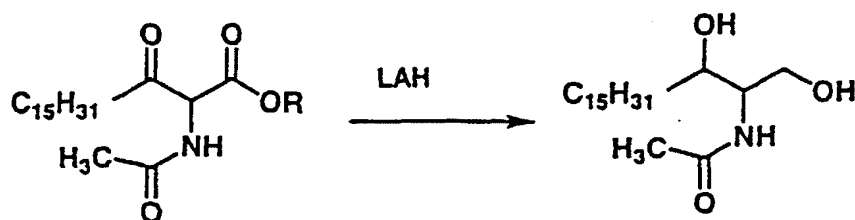
Fig. 12 shows the comparison of the rate of water loss between a racemate, its optical isomer and a pseudoceramide, effected by using the compositions 34 to 37.

The 2-acetaminoalkane-1,3-diol and 2-acylaminoalkane-1,3-diol used in the present invention may be prepared by a chemical synthesis. They can be either a racemate substance, a natural-type optical isomer or a non-natural-type optical isomer, or further still a combination thereof.

In 2-acetaminoalkane-1,3-diol where R1 indicates a linear alkyl group having 11 to 17 carbon atoms, R1 may typically have 15 carbon atoms. Then, the product may be either a racemate of 2-acetaminooctadecane-1,3-diol, natural optical isomer (2S, 3R)-2-acetaminooctadecane-1,3-diol, a non-natural optical isomer (2S, 3S)-, (2R, 3R)- or (2R, 3S)-2-acetaminooctadecane-1,3-diol, or a mixture thereof. However, the 2-acetaminooctadecane-1,3-diols which can be used for the purpose of the invention are not limited to the above-mentioned products and extend to substances having various number and configuration of carbons defined in the invention.

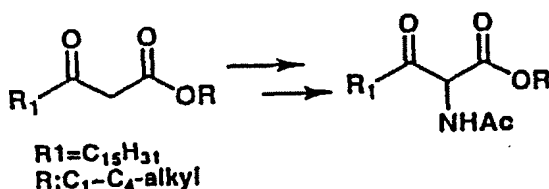
The racemate can be prepared by acetylating commercially available 2-aminooctadecane-1,3-diol. It can also be obtained according to the method described by D. SHAPIRO et al. in J. Am. Chem. Soc., 80, 2170, 1958.

As can be seen, ester and ketone groups in an ester of 2-acetamino-3-oxooctadecanoic acid are reduced in the presence of lithium aluminium hydride (referred to as LAH) to give a racemate of 2-acetaminooctadecane-1,3-diol, as follows:



Although this racemate can form a liquid crystal necessary for the purpose of the present invention, it crystallizes rather rapidly, so that the crystals formed are not sufficiently stable. For this reason, the racemate has a lower moisture-retaining capacity than its corresponding optically active isomers.

In order to obtain optically active isomers of the component A (I), an ester of 2-acetamino-3-oxoalkanoic acid is prepared beforehand according to the method of D. SHAPIRO described in J. Am. Chem. Soc., 80, 2170, 1958, as follows:

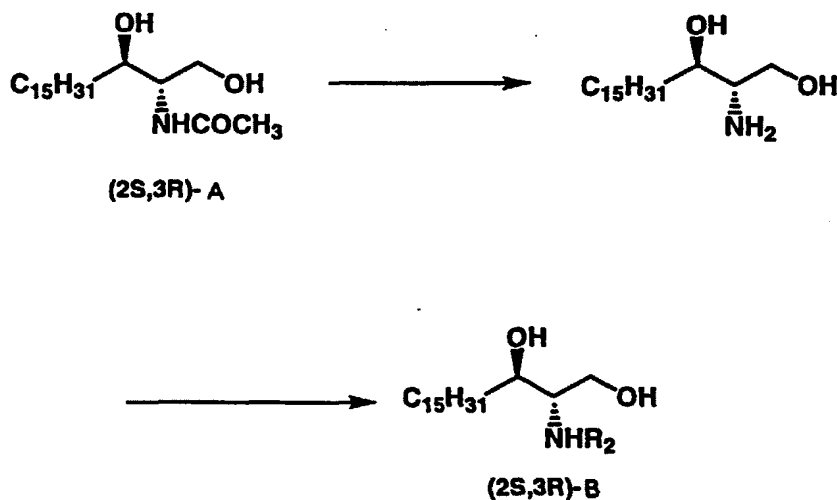


This product is asymmetrically hydrogenized in the presence of a complex of ruthenium and optically active phosphine, e.g. (-)-phosphine, to give the ester of (2R, 3S)-2-acetamino-3-hydroxyalkanoic acid, for example, as described in Japanese Unexamined Patent Application Hei 6-80 617.

The latter product is then allowed to react with thionylchloride to invert the steric configuration of the hydroxy group and to give the ester of (2R, 3R)-2-acetamino-3-hydroxyalkanoic acid. The ester group is subsequently reduced in the presence of sodium borohydride to give the (2S, 3R)-2-acetaminoalkane-1,3-diol sought-after. If the hydroxy group is not sterically inverted, (2S, 3S)-type substance is obtained. Further, if (+)-phosphine is used in the ruthenium-phosphine complex instead of (-)-type, (2R, 3R)- and (2R, 3S)-types are obtained. This process is summarized in Fig. 1.

Typical examples of the component A having formula (I) include a racemic or optically active substance of aminodiol derivative such as 2-acetaminododecane-1, 3-diol, 2-acetaminotridecane-1, 3-diol, 2-acetaminotetradecane-1, 3-diol, 2-acetaminopentadecane-1, 3-diol, 2-acetaminohexadecane-1, 3-diol, 2-acetaminoheptadecane-1, 3-diol, 2-acetaminooctadecane-1, 3-diol, 2-acetaminononadecane-1, 3-diol, 2-acetaminoeicosane-1, 3-diol, or the like.

The component B having formula (II) of the present invention may be obtained by de-acetylating the corresponding racemic or optically active component A (I) to give the corresponding 2-aminoalkane-1, 3-diol (dihydrosphingosine), then by acylating the latter with an appropriate acylating agent, as follows:



The acylating agent may include, for example, a commercially available higher fatty acid and a derivative thereof such as a fatty acid halide, a fatty acid anhydride, anhydride of mixed fatty acids, a fatty acid ester, p-nitrophenyl ester of a fatty acid, N-hydroxysuccinimide ester of a fatty acid, or the like.

Typically, the acylating agent may be tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, heptadecanoic acid, octadecanoic acid, nonadecanoic acid, eicosanoic acid, or chloride, anhydride of a single or mixed fatty acids, p-nitrophenol ester, N-hydroxysuccinimide ester or a lower alkyl ester prepared therefrom.

Typical examples of the component B include a racemic or optically active substance of 2-tetradecanoylamino-octadecane-1, 3-diol, 2-pentadecanoylamino-octadecane-1, 3-diol, 2-hexadecanoylamino-octadecane-1, 3-diol, 2-heptadecanoylamino-octadecane-1, 3-diol, 2-octadecanoylamino-octadecane-1, 3-diol, 2-nonadecanoylamino-octadecane-1, 3-diol, 2-eicosanoylamino-octadecane-1, 3-diol, 2-heneicosanoylamino-octadecane-1, 3-diol, 2-docosanoylamino-octade-

cane-1, 3-diol, 2-tricosanoylaminoctadecane-1, 3-diol, or 2-tetracosanoylaminoctadecane-1, 3-diol.

When R2 in the component B is the acyl group having a hydroxy group on the position of carbon-2, the acylating agent used may be a commercially available higher fatty acid having a hydroxy group protected by a group such as acetyl group. The higher fatty acid may contain a halide, anhydride of a single or mixed fatty acids and an ester such as p-nitrophenol ester. It is also possible to use, as an acylating agent, an ester of higher fatty acid in which the hydroxy group is not protected.

Typical examples of the acylating agent include 2-hydroxytri-, tetra-, penta-, hexa-, hepta-, octa-, or nona-decanoic acid, 2-hydroxyeicosanoic acid, 2-hydroxydocosanoic acid, 2-hydroxytricosanoic acid, 2-hydroxytetracosanoic acid, or an acetylated form of chloride, anhydride, mixed anhydride, p-nitrophenyl ester, N-hydroxysuccinimide and a lower-carbon ester thereof. When 2-hydroxy fatty acid is esterified with an alkyl group having 1 to 4 carbon atoms, acylation may be carried out without the hydroxy group being protected by an acetyl group. The resulting product is then a corresponding racemic or optically active 2-hydroxy derivative such as (2S, 3R)-2- (2-hydroxytetra-, penta-, hexa-, hepta-, octa-, nona-decanoyl- or eicosanoyl-, docosanoyl-, tricosanoyl-, or tetracosanoyl-amino) octadecane-1, 3-diol, etc..

When R2 in the component B is a 2-oleoyl group, the acylating agent used may be either a commercially available, high purity cis-9-octadecenoic acid (oleic acid of 99 % or 91 % purity by weight, produced by NOF Corporation) or a commercially available reagent of cis-9-octadecenoic acid (oleic acid of 75 to 85 % purity by weight, produced by NOF Corporation, Nakalai Tesque, Tokyo Kasei, etc.). It may also be cis-9-octadecenoyl chloride, cis-9-octadecenoyl p-nitrophenyl, cis-9-octadecenoyl N-hydroxysuccinimide, a lower alkyl ester of cis-9-octadecenoic acid, etc., prepared therefrom.

When the high-purity cis-9-octadecenoic acid is used, the resultant product is mainly a corresponding racemic or optically active derivative such as (2S, 3R)-2-(cis-9-octadecenoylamino) dodecane-, tridecane-, tetradecane-, pentadecane-, hexadecane-, heptadecane-, octadecane-, nonadecane-, or eicosane-1, 3-diol, etc..

The commercial reagent of cis-9-octadecenoic acid (oleic acid) has a purity of about, or a little higher than, 70 % by weight and contains the impurities such as tetradecanoic acid, hexadecanoic acid, cis-9-hexadecenoic acid, octadecanoic acid, cis, cis-9, 12-octadecadienoic acid, etc., or a derivative thereof.

Accordingly, when this commercial reagent or its derivative is used to synthesize 2-cis-9-octadecenoylaminoalkane-1, 3-diol, the resultant products contain not only (2S, 3R)-2-cis-9-octadecenoylaminoalkane-1, 3-diol as the main product, but also dihydroceramides as by-products, which are formed by the amide-bonding of the impurities with 2-aminoalkane-1, 3-diol. These by-products include (2S, 3R)-2-tetradecanoylaminoalkane-1, 3-diol, (2S, 3R)-2-hexadecanoylaminoalkane-1, 3-diol, (2S, 3R)-2-octadecanoylaminoalkane-1, 3-diol, (2S, 3R)-2-(cis-9-hexadecenoylamino) alkane-1, 3-diol, (2S, 3R)-2-octadecanoylaminoalkane-1, 3-diol, (2S, 3R)-2-(cis, cis-9, 12-octadecadienoylamino) alkane-1, 3-diol, etc.. A mixture of these cis-9-octadecenoic acid-derived products having 14 to 18 saturated or unsaturated carbon atoms are collectively called as (2S, 3R)-2-oleoylaminoalkane-1, 3-diol.

Sterol used is preferably cholesterol. Cholesterol may be of animal- or plant-origin. It may also be a commercially available synthetic cholesterol having a high purity such as the one produced by Nakalai Tesque.

The fatty acid used may be tetradecanoic acid (myristic acid), hexadecanoic acid (palmitic acid), octadecanoic acid (stearic acid), hydroxyoctadecanoic acid (hydroxystearic acid), isostearic acid or the like. Amongst them, isostearic acid is preferred. The fatty acid having a higher carbon content may be a commercially available product. Isostearic acid used may be a commercially available 2-(1, 3, 3-trimethylbutyl)-5, 7, 7-trimethyloctanoic acid.

To form a liquid crystal structure, the appropriate proportion of the component A, the component B, the cholesterol (component C) and optionally an additive to be mixed may vary depending on the kind and purity of the components A, B and C and the additive used. However, this proportion can be determined very easily by carrying out experiments with a chosen composition. Usually, 2-acetaminoalkane-1 3-diol (component A) plays an important role for forming a lamellar liquid crystal. Without using the component A, it can be difficult to form a stable lamellar liquid crystal structure..

When three components, i.e. a (2S, 3R)-2-acetaminoalkane-1, 3-diol (A), a (2S, 3R)-2-oleoylaminoalkane-1, 3-diol (B) and cholesterol (C) are used, the weight proportions of A to B, B to C and A to C may range from 1 : 1 to 1 : 8, from 7 : 1 to 1 : 1 and from 1 : 1 to 1 : 3, respectively.

More specifically, when (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A), (2S, 3R)-2-oleoylaminooctadecane-1, 3-diol (B) and cholesterol (C) are used, the weight proportions of A to B and B to C preferably range from 1 : 1 to 1 : 8 and from 7 : 1 to 1 : 1, respectively.

When (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A), (2S, 3R)-2-oleoylaminohexadecane-1, 3-diol (B) and cholesterol (C) are used, the weight proportions of A to B and B to C preferably range from 1 : 6 to 1 : 3 and from 6 : 1 to 3 : 2, respectively.

When (2S, 3R)-2-acetaminohexadecane-1, 3-diol (A), (2S, 3R)-2-oleoylaminooctadecane-1, 3-diol (B) and cholesterol (C) are used, the weight proportions of A to B and B to C preferably range from 1 : 5 to 2 : 5 and 5 : 1 to 1 : 1, respectively.

When (2S, 3R)-2-acetaminohexadecane-1, 3-diol (A), (2S, 3R)-2-oleoylhexadecane-1, 3-diol (B) and cholesterol (C) are mixed, the weight proportions of A to B and B to C preferably range from 1 : 4 to 1 : 1 and from 3 : 1 to 1 : 1,

respectively.

When (2S, 3R)-2-acetaminotetradecane-1, 3-diol (A), (2S, 3R)-2-oleoylaminoctadecane-1, 3-diol (B) and cholesterol (C) are mixed, the weight proportions of A to B and B to C preferably range from 1 : 1 to 1 : 4 and from 2 : 1 to 1 : 1, respectively.

The optionally added additive according to the invention may be a cholesterol ester. Typical examples of the cholesterol ester are cholesteryl oleate, cholesteryl stearate, cholesteryl hydroxystearate, cholesteryl isostearate, or the like. These products can be synthesized chemically and are commercially available as high purity products. Amongst them, cholesteryl hydroxystearate is preferably used. Such a product is the commercially available as cholesteryl 12-hydroxystearate, produced by Nisshin Seiyu under the name of "Sarakosu HS".

When four components, i.e. (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A), (2S, 3R)-2-octadecanoylaminoalkane-1, 3-diol (B), cholesterol (C) and cholesteryl hydroxystearate (D) are used, the weight proportions of A to B, B to C and C to D preferably range from 1 : 1 to 2 : 5, from 2 : 1 to 1 : 2 and from 3 : 1 to 1 : 1, respectively.

When (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A), (2S, 3R)-2-hexadecanoylaminoalkane-1, 3-diol (B), cholesterol (C) and cholesteryl hydroxystearate (D) are mixed, the weight proportions of A to B, B to C and C to D preferably range from 1 : 1 to 1 : 3, from 2 : 1 to 1 : 2 and from 3 : 1 to 1 : 1, respectively.

Alternatively, in order to draw a phase equilibrium diagram with three poles, the components (A) and (B) may be mixed in a fixed ratio before being combined with the other components C and D.

Thus, racemic 2-acetaminoalkane-1, 3-diol (A) and racemic 2-acylaminoalkane-1, 3-diol (B) are mixed (A+B) in a weight proportion ranging from 1 : 1 to 1 : 2, then combined with cholesterol (C) and cholesteryl hydroxystearate (D). Then, the weight proportion of A+B to C preferably ranges from 5 : 4 to 5 : 1, but is more preferably in the range of 3 : 2 to 2 : 1, whilst the weight proportion of C to D preferably ranges from 4 : 1 to 1 : 5, but is more preferably in the range of 2 : 1 to 1 : 1.

For example, when (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A) and (2S, 3R)-2-octadecanoylaminoctadecane-1, 3-diol (B) are mixed (A+B) in a weight proportion ranging from 1 : 1 to 1 : 2, then combined with cholesterol (C) and cholesteryl hydroxystearate (D), the preferable proportion range of A+B to C, and C to D is the same as mentioned above.

The optionally added additive according to the invention may also be a fatty acid having a higher carbon atom content, preferably isostearic acid. Isostearic acid may be the product made by Wako Junyaku.

When (2S, 3R)-2-acetaminohexadecane-1, 3-diol (A), (2S, 3R)-2-(2'-hydroxyhexadecanoylamino) hexadecane-1, 3-diol (B), cholesterol (C) and isostearic acid (D) are mixed, the weight proportions of A to B, B to C and C to D preferably range from 1 : 4 to 2 : 7, from 4 : 1 to 7 : 1, and from 1 : 1 to 1 : 4, respectively.

When (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A), (2S, 3R)-2-(2'-hydroxyhexadecanoyl) octadecane-1, 3-diol (B), cholesterol (C) and isostearic acid (D) are mixed, the weight proportions of A to B, B to C and C to D preferably range from 1 : 1 to 1 : 4, from 4 : 1 to 1 : 2 and from 1 : 1 to 1 : 5, respectively.

Alternatively, racemic 2-acetaminooctadecane-1, 3-diol (A) and racemic 2-(2'-hydroxyhexadecanoyl) aminooctadecane-1, 3-diol (B), when mixed in a weight proportion of 1 : 4, form a stable liquid crystal structure together with cholesterol (C) and isostearic acid (D). The weight proportion of A+B to C preferably ranges from 5 : 1 to 3 : 1, but is more preferably around 5 : 1, whilst the weight proportion of C to D preferably ranges from 1 : 1 to 1 : 4, but is more preferably in the range of 1 : 3 to 1 : 4.

Also, (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A) and (2S, 3R, 2'RS)-2-(2'-hydroxyhexadecanoyl) aminooctadecane-1, 3-diol (B), when mixed in a weight proportion of either 1 : 2, 1 : 5 or 1 : 8, form a stable liquid crystal structure together with cholesterol (C) and isostearic acid (D).

In the first mixture, i.e. A : B = 1 : 2, the preferable range of (A + B) to C is around 5 : 1, whilst that of C to D varies from 1 : 1 to 1 : 4, but more preferably 1 : 1 to 1 : 3. In the second mixture, i.e. A : B = 1 : 5, the preferable range of (A + B) to C varies from 5 : 1 to 3 : 1, but is more preferably around 5 : 1, whilst that of C to D varies from 1 : 1 to 1 : 4, but is more preferably around 1 : 1. In the third mixture, i.e. A : B = 1 : 8, the preferable range of (A + B) to C is around 5 : 1, whilst that of C to D varies from 1 : 1 to 1 : 4, but is more preferably around 1 : 4.

To cite an example, Fig. 5 also includes the phase equilibrium obtained for a mixture of (2S, 3R)-2-acetaminohexadecane-1, 3-diol and of (2S, 3R)-2-(2'-hydroxyhexadecanoylamino) octadecane-1, 3-diol; cholesterol (C) and isostearic acid (D).

Preferably, a triglyceride is added to the composition of the invention. Its addition can stabilize, and prolong the life of, the liquid crystal or lamellar liquid crystal structure.

Typical examples of the triglyceride include commercially available glyceryl tricaprinate, glyceryl tricaprilate, glyceryl trioleate, glyceryl tri-2-ethylhexanoate, etc.. The amount of glyceride used preferably ranges from 5 to 10 % by weight of the composition.

Formation of the liquid crystal or lamellar liquid crystal structure is verified by the method of MIZUSHIMA et al. described in Yu Kagaku, p. 656, 1994. According to this method, associative mechanism and phase behaviour of the composition are observed through a polarizing microscope and analyzed through X-ray diffraction and differential scan-



ning calorimetry.

The above-mentioned composition may also comprise a cosmetic or pharmaceutical medium, so that it can be used as a cosmetic product, a hair-protecting product or a bath additive.

To prepare such a product, a preferred method is to first mix the aforementioned components and / or glyceride in a predetermined proportion, dissolve the mixture by heating and cool it down in order to give a paste. The paste is then added to a cosmetic or pharmaceutical medium.

The cosmetic or pharmaceutical product may be prepared in the form of an emulsion such as a milky lotion, cream, shampoo, etc., or a lotion where the hydrophilic solution and the lipophilic solution are separated.

The content of the composition to be added to a cosmetic or pharmaceutical product is not specifically restricted. In the case of an emulsion, the amount used can range preferably from 0.001 to 10 %, more preferably from 0.01 to 5 %, still more preferably from 0.02 to 3 % by weight of composition.

The emulsion can be in the form of water phase surrounded by lipid phase or vice versa, the lipid phase being the composition according to the invention. In this case, the lipid phase can account for 5 to 60 % by weight of the total emulsion, the water phase 30 to 85 % and the emulsifier 1 to 20 %, preferably 2 to 12 %.

Examples of the composition for use in baths, for the purpose of the invention, may include bath oil, bath salt and body shampoo.

Examples of the hair-protecting composition may include a cosmetic product for hair washing such as shampoo, hair rinse, etc., a hair-dressing product such as hair liquid, hair cream, hair spray, etc. and a hair restorer such as hair tonic or other hair treatment product.

For use in baths and hair washing, there is no specific restriction for the concentration of the composition to be contained in the product. However, it is usually 0.01 to 10 %, preferably 0.01 to 5 % by weight of the total product.

The composition according to the invention can also be used for preparing a foundation, a lipstick and a skin cream, by virtue of its moisture-retaining capacity.

When the composition according to the invention is used for a cosmetic or pharmaceutical product, it gives the same effect as a known natural ceramide extracted from a bovine brain.

## EXAMPLES

### PREPARATION OF THE COMPOSITIONS

The compositions according to the invention were prepared by mixing components A, B and C, optionally together with component D, in a weight proportion as indicated hereinafter. In the description below, racemic 2-acetaminoalkane-1, 3-diol and its (2S, 3R) isomer are replaced respectively by letter A and (2S, 3R)-A, whilst racemic 2-acylaminoalkane-1, 3-diol and its (2S, 3R) isomer by letter B and (2S, 3R)-B. Component C means "cholesterol". When component D is used, it is indicated in parentheses.

- composition 1: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C15H31 and R2 is C17H33CO : C = 2 : 6 : 3. In this preparation, the component B used had a purity in excess of 75%.
- composition 2: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C13H27 and R2 is C17H33CO : C = 2 : 5 : 3. The component B used had a purity in excess of 75 %.
- composition 3 : (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C13H27 and R2 is C17H33CO : C = 2 : 4 : 3. The component B used had a purity in excess of 75 %.
- composition 4: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R2 is C15H31 and R3 is C17H33CO : C = 1 : 3 : 2. The component B used had a purity in excess of 75 %.
- composition 5: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C15H31 and R2 is C17H35CO : C : D (cholesteryl hydroxystearate) = 1 : 2 : 2 : 1.
- composition 6: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C15H31 and R2 is C17H35CO : C : D (cholesteryl hydroxystearate) = 2 : 2 : 3 : 1.
- composition 7: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C13H27 and R2 is C15H31CO : C : D (cholesteryl hydroxystearate) = 1 : 3 : 2 : 1.
- composition 8: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C15H31 and R2 is C15H31CO : C : D (cholesteryl hydroxystearate) = 2 : 4 : 3 : 3.
- composition 9: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C17H35 and R2 is C17H35CO : C : D (cholesteryl hydroxystearate) = 2 : 2 : 3 : 1.
- composition 10: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C17H35 and R2 is C15H31CO : C : D (cholesteryl hydroxystearate) = 1 : 2 : 2 : 1.
- composition 11: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C11H23 and R2 is C17H35CO : C : D (cholesteryl hydroxystearate) = 2 : 2 : 3 : 1.

- composition 12: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C13H27 and R2 is C17H35CO : C : D (cholesteryl hydroxystearate) = 2 : 4 : 3 : 3.
- composition 13: A in which R1 is C15H31 : B in which R1 is C15H31 and R2 is C14H29CH(OH)CO = 1 : 5. (A + B) : C : D (isostearic acid) = 5 : 1 : 4.
- 5 - composition 14: A in which R1 is C15H31 : B in which R1 is C15H31 and R2 is C12H25CH(OH)CO = 1 : 6. (A + B) : C : D (isostearic acid) = 5 : 1 : 3.
- composition 15: A in which R1 is C13H27 : B in which R1 is C15H31 and R2 is C14H29CH(OH)CO = 1 : 4. (A + B) : C : D (isostearic acid) = 5 : 1 : 3.
- composition 16: A in which R1 is C13H27 : B in which R1 is C15H31 and R2 is C16H33CH(OH)CO = 1 : 3. (A + B) : C : D (isostearic acid) = 3 : 1 : 4.
- 10 - composition 17: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C15H31 and R2 is C14H29CH(OH)CO : C : D (isostearic acid) = 1 : 4 : 1 : 4.
- composition 18: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C13H27 and R2 is C14H29CH(OH)CO : C : D (isostearic acid) = 1 : 4 : 1 : 4.
- 15 - composition 19: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C15H31 and R2 is C14H29CH(OH)CO : C : D (isostearic acid) = 1 : 4 : 1 : 4.
- composition 20: (2S, 3R)-A in which R1 is C15H31 : (2S, 3R)-B in which R1 is C15H31 and R2 is C16H33CH(OH)CO : C : D (isostearic acid) = 1 : 4 : 1 : 4.
- composition 21: (2S, 3R)-A in which R1 is C13H27 : (2S, 3R)-B in which R1 is C13H27 and R2 is C14H29CH(OH)CO : C : D (isostearic acid) = 1 : 4 : 1 : 3.
- 20 - composition 22: A in which R1 is C15H31 : B in which R1 is C15H31 and R2 is C17H35CO = 1 : 1. (A + B) : C : D (cholesteryl hydroxystearate) = 4 : 3 : 1.
- composition 23: A in which R1 is C15H31 : B in which R1 is C15H31 and R2 is C13H27CO = 1 : 2. (A + B) : C : D (cholesteryl hydroxystearate) = 3 : 2 : 1.
- 25 - composition 24: A in which R1 is C13H27 : B in which R1 is C15H31 and R2 is C17H35CO = 1 : 1. (A + B) : C : D (cholesteryl hydroxystearate) = 4 : 3 : 1.
- composition 25: A in which R1 is C13H27 : B in which R1 is C15H31 and R2 is C15H31CO = 1 : 1. (A + B) : C : D (cholesteryl hydroxystearate) = 4 : 2 : 1.

### 30 OBSERVATION OF LAMELLAR LIQUID CRYSTAL STRUCTURE

Apparatus used were:

- Differential scanning calorimeter DSC 220, manufactured by Seiko Instrument Inc.;
- 35 - Small angle X-ray scattering device PW 3050, manufactured by Philips Japan Ltd.;
- Polarizing microscope, manufactured by Olympus Optical Co.;

A composition according to the invention was completely melted by heating above the melting temperature and stirred vigorously. The melted composition became a uniform, transparent liquid. After this was observed, the liquid  
40 was allowed to stand in room temperature and further at 25 °C for one to two hours, to give a solid product.

About 10 mg of product were sampled in a sealable silver pan and analyzed by DSC at a heating rate of 2 °C / min, in order to observe the phase transition of the composition.

On the other hand, a composition was melted at a temperature ranging from 120 to 140 °C. When the melt was cooled, it generated heat at about 72 °C while maintaining the state of super-cooled liquid. It was then transformed into  
45 a liquid crystal state. The liquid crystal state was analyzed by X-ray diffraction just after the formation of liquid crystal and 15 days later. Diffraction peaks were observed at regular intervals at the low angle region: 41.8 Å (2 θ = 2.2°), 20.6 Å (2 θ = 4.3°), 13.4 Å (2 θ = 6.6°) and 10.2 Å (2 θ = 8.6°) and peak ratio was 1 : 1 / 2 : 1 / 3 : 1 / 4. There was also observed a blurred halo at 4.5 Å. These observations indicate that the structure obtained was a lamellar liquid crystal.

The compositions 1 to 25 were observed on a polarizing microscope to study the associated state of the phase.  
50 The phase behaviour was analyzed by DSC and the structure by a small angle X-ray scattering device. The results indicated that the compositions formed a lamellar liquid crystal structure.

The stability of the obtained lamellar liquid crystal was tested, for example, with the following compositions:

- composition 1: (2S, 3R)-2-acetaminoalkane-1, 3-diol (A) and (2S, 3R)-2-acylaminoalkane-1, 3-diol (B) mixed in a  
55 proportion ranging from 1 : 1 to 1 : 3 and components B to cholesterol (C) in a weight proportion ranging from 2 : 1 to 1 : 1;
- composition 5: (2S, 3R)-2-acetaminoalkane-1, 3-diol (A) and (2S, 3R)-2-acylaminoalkane-1, 3-diol (B) mixed in a weight proportion ranging from 1 : 2 to 1 : 1; components (A + B) and cholesterol (C) in a weight proportion ranging

from 3 : 2 to 2 : 1; and the component (C) and cholesteryl hydroxystearate (D) in a weight proportion ranging from 2 : 1 to 1 : 1.

- composition 17: (2S, 3R)-2-acetaminoalkane-1, 3-diol (A) and (2S, 3R)-2-acylaminoalkane-1, 3-diol (B) mixed in a weight proportion ranging from 1 : 2 to 1 : 8; components (A + B) and cholesterol (C) in a weight proportion of 5 : 1; and the component (C) and isostearic acid (D) in a weight proportion ranging from 1 : 1 to 1 : 4;

The product thus obtained maintained a lamellar liquid crystal structure even after 14 days, without crystallizing.

However, the object of the invention is not limited to the above-mentioned weight proportion. To form a desired liquid crystal structure, the components A, B, C and optionally D, may be mixed in the range defined in ternary phase equilibrium diagrams. These diagrams, shown in Figs. 2 to 6, thus define a preferable range of the components to be added, in order to form a liquid crystal phase.

Fig. 2 shows a ternary phase equilibrium diagram established by using (2S, 3R)-2-acetaminoalkane-1, 3-diol (A), (2S, 3R)-2-oleoylaminoalkane-1, 3-diol (B) and cholesterol (C), where the marks  $\odot$ , O and x respectively indicate very stable, stable and unstable lamellar liquid crystal domain;

Fig. 3 shows a ternary phase equilibrium diagram established by using a mixture of (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A) and (2S, 3R)-2-octadecanoylaminoalkane-1, 3-diol (B), cholesterol (C) and cholesteryl hydroxystearate (D), where the marks O,  $\diamond$  and  $\blacklozenge$  indicate the formation of stable lamellar liquid crystal when A and B are mixed in a proportion of 1 : 1, 1 : 2 and both of 1 : 1 and 1 : 2, respectively;

Fig. 4 shows a ternary phase equilibrium diagram established by using a mixture of 2-acetaminoalkane-1, 3-diol (A) and 2-acylaminoalkane-1, 3-diol (B), cholesterol (C) and isostearic acid (D), where the compositions used include those of No. 13 to 16 described in "Examples" and where the mark  $\blacklozenge$  indicates the domain of lamellar liquid crystal formed;

Fig. 5 shows a ternary phase equilibrium diagram established by using a mixture of (2S, 3R)-2-acetaminohexadecane-1, 3-diol (A) and (2S, 3R)-2-(2-hydroxyhexadecanoylamino) octadecane-1, 3-diol (B), cholesterol (C) and isostearic acid (D), where the compositions used include those of No. 17 to 21 described in "Examples" and where the mark  $\blacklozenge$  indicates the domain of lamellar liquid crystal formed;

Fig. 6 shows a ternary phase equilibrium diagram established by using a mixture of 2-acetaminoalkane-1, 3-diol (A) and 2-acylaminoalkane-1, 3-diol (B), cholesterol (C) and cholesteryl hydroxystearate (D), where the marks O,  $\diamond$  and  $\blacklozenge$  indicate the formation of stable lamellar liquid crystal when the components A and B are mixed in a proportion of 1 : 1, 1 : 2 and both of 1 : 1 and 1 : 2, respectively;

#### WATER-RETENTION TEST 1

Samples 1 to 4 were prepared by mixing ingredients by weight % as indicated for each sample hereinbelow. Each sample contained at least 2.0 g of purified water. The samples were allowed to stand at 37 °C in a humidity of 35 + or - 2 % and water evaporation was measured for each sample at every 30 minutes. .

- sample 1: 10 % of composition 1, 2 % of Decaglyn 1-M\* and 88 % of purified water;
- sample 2: 10 % of composition 1 and 90 % of purified water;
- sample 3: 2 % of Decaglyn 1-M and 98 % of purified water
- sample 4: 100 % of purified water.

The results are shown in Fig. 7, where "100 % of water-retention ratio" means no water loss and "0 %", total water loss. As seen here, in sample 3 which contains 2 % Decaglyn 1-M and 98 % of water, the ratio became 0 % after 4 to 5 hours. In comparison, in sample 2 which contains 10 % of composition 1, the ratio was 8 % after 7 hours. In sample 1 where composition 1 was further supplemented with 2 % of Decaglyn 1-M, the figure was 35 % after 7 hours.

#### WATER-RETENTION TEST 2

Samples 5 to 10 were prepared and tested as described in water-retention test 1:

- sample 5: 10 % of the composition 5, 1 % of Decaglyn 1-M and 89 % of purified water;
- sample 6: 10 % of the composition 5 and 90 % of purified water;
- sample 7: 10 % of glycerine, 1 % of Decaglyn 1-M and 89 % of purified water;
- sample 8: 10 % of glycerine and 90 % of purified water;
- sample 9: 1 % of Decaglyn 1-M and 99 % of purified water;

\* trade name of decaglyceryl monomyristate, produced by Nikko Chemical Co. Ltd..

- sample 10: 100 % of purified water;

As seen in Fig. 8, samples 7 to 9, in which 10 % of glycerine and/or 1 % of Decaglyn 1-M are added to the purified water, show 0 % water retention after 3 to 5 hours. In comparison, in sample 6 containing 10 % of composition 5 of the invention, it took more than 6 hours to reach 0 % retention. Moreover, in sample 5 containing 10 % of the composition 5 and 1 % of Decaglyn 1-M, it retained about 23 % of water after 7 hours of run, and still about 15 % after 10 hours.

Test effected with compositions 17 and 22 yielded essentially the same results.

Fig. 9 shows a result when composition 13 is used. In sample 6 containing 10 % of this composition, it took more than 6 hours to reach 0 % water retention. Moreover, in sample 5 which further contains 1 % of Decaglyn 1-M, it retained about 15 % of water after 10 hours.

#### COMPARISON BETWEEN A RACEMIC AND AN OPTICALLY ACTIVE COMPOSITION

Compositions 26 and 27 were prepared from the four components as indicated below, except that in composition 26 an optically active ceramide was used instead of the racemate:

- composition 26:

(2S, 3R)-2-oleoylamino-octadecane-1, 3-diol	120 mg
cholesterol	75 mg
palmitic acid	75 mg
cholesteryl sodium sulphate	30 mg

- composition 27:

racemic 2-oleoylamino-octadecane-1, 3-diol	120 mg
cholesterol	75 mg
palmitic acid	75 mg
cholesteryl sodium sulphate	30 mg

20 g each of compositions 26 and 27 were prepared. Ten fractions of 50 mg were sampled from each composition and put into ten corresponding sample bottles (S-08 type). Each bottle was supplemented with 200  $\mu$ l of water, annealed at 90 °C for 10 minutes and allowed to stand one night at - 20 °C. The procedure of annealing and freezing was repeated three times, to obtain samples 26 and 27, each grouping 10 bottles. The bottles were put into an incubator adjusted at 40 °C. Loss of weight (water loss) of each bottle was measured hourly over nine hours and the average water-loss rate of the ten bottles for each sample was plotted and shown in Fig. 10.

The water-loss rate for sample 26 was 23.6 % after 10 hours and 55 % after 24 hours, whilst the corresponding figures for sample 27 were respectively 27.2 % and 63 %. It can therefore be said that, when preparing a composition similar to intercellular lipids in stratum corneum, (2S, 3R)-type optical isomer yields a better moisture-retaining capacity than its racemate.

Likewise, compositions 28 and 29 were prepared by using (2S, 3R)-2-(octadecanoylamino) octadecane-1, 3-diol and its racemate, instead respectively of (2S, 3R)-2-oleoylamino-octadecane-1, 3-diol of composition 26 and its racemate of composition 27. Samples 28 and 29 were then prepared therefrom and tested for rate of water loss as described above. The result was substantially the same as that shown in Fig. 10.

#### COMPARISON WITH A PSEUDOCERAMIDE

Samples were prepared from the corresponding compositions described below, according to the method mentioned in "comparison between a racemic and an optically active composition". The samples were then tested for rate of water loss. Proportion is indicated by weight.

- composition 30: (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A) : (2S, 3R)-2-(cis-9-octadecenoylamino) octadecane-1, 3-diol, i.e. (2S, 3R)-2-oleoylaminoctadecane-1, 3-diol (B) : cholesterol (C) = 2 : 6 : 3;
- composition 31: (2S, 3R)-2-acetaminohexadecane-1, 3-diol (A) : (2S, 3R)-2-oleoylaminoctadecane-1, 3-diol (B) : cholesterol (C) = 2 : 6 : 3;
- 5 - composition 32: racemic 2-acetaminooctadecane-1, 3-diol (A) : racemic 2-oleoylaminoctadecane-1, 3-diol (B) : cholesterol (C) = 2 : 6 : 3;
- composition 33: cholesteryl isostearate : stearic acid : cholesterol : a pseudoceramide = 1 : 6 : 3 : 10, in which the pseudoceramide is N-(3-hexadecyloxy-2-hydroxypropyl)-N-2-hydroxyethylhexadecaamide.

10 Fig. 11 shows that optically active compositions 30 and 31 have a better water-retention capacity than the corresponding racemic composition 32 or composition 33 comprising a pseudoceramide.

The same preparation and test were carried out using the following compositions:

- composition 34: (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A) : (2S, 3R)-2-octadecanoylaminoctadecane-1, 3-diol (B) : cholesterol (C) : cholesteryl hydroxystearate (D) = 1 : 2 : 2 : 1;
- 15 - composition 35: (2S, 3R)-2-acetaminooctadecane-1, 3-diol (A) : (2S, 3R)-2-hexadecanoylaminoctadecane-1, 3-diol (B) : cholesterol (C) : cholesteryl hydroxystearate (D) = 1 : 2 : 2 : 1;
- composition 36: racemic 2-acetaminooctadecane-1, 3-diol (A) : racemic 2-octadecanoylaminoctadecane-1, 3-diol (B) : cholesterol (C) : cholesteryl hydroxystearate (D) = 1 : 2 : 2 : 1;
- 20 - composition 37: the pseudoceramide : cholesterol : cholesteryl isostearate : stearic acid = 10 : 3 : 1 : 6.

Fig. 12 shows the result obtained, which indicates substantially the same tendency as that shown in Fig. 11.

#### PREPARATION OF CREAM

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##### Cream 1

Composition 1, 5 or 17 was dissolved in a water phase consisting of purified water and propylene glycol by heating at 70 °C, to obtain a hydrated liquid crystal. An oily phase was prepared by mixing the other ingredients indicated below and dissolving by heating at 70 °C. The oily phase was added to the hydrated liquid crystal at 70 °C. The mixture was vigorously stirred by homogenizer, thereby obtaining a white cream having small oily micelles dispersed in the aqueous phase.

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Ingredients, % by weight:	
- composition 1, 5 or 17	1.5
- $\alpha$ -tocopherol acetate	0.3
- liquid paraffin	5.0
- silicone oil	1.0
- bleached beeswax	1.0
- cetyl octanoate	1.5
- stearic acid	2.4
- cetyl alcohol	4.0
- polyethyleneglycol monostearate	1.4
- glyceryl monostearate	2.4
- propyleneglycol	5.0
- glycerine	10.0
- perfume	0.05
- paraben	0.2
- purified water	remainder

## EP 0 875 232 A1

### Cream 2

Some ingredients of cream 1 were replaced by the ingredients indicated below:

- composition 1, 5 or 17; 1.5 %, by composition 13 or 22; 0.4 %;
- bleached beeswax; 1.0 %, by beeswax; 1.0 %; and,
- propyleneglycol; 5.0 %, by 1,3-butyleneglycol; 5.0 %.

In addition, a following ingredient was added:

- glyceryl tri-(2-ethylhexanoate), 0.02 %.

### PREPARATION OF PROTECTIVE CREAM

- To prepare the protective cream, the method mentioned for the cream was applied mutatis mutandis.

#### Protective cream 1

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Ingredients, % by weight:	
- composition 5	1.0
- bleached beeswax	1.0
- 1,3-butylene glycol	5.0
- cetyl octanoate	1.5
- squalane	30.0
- cetyl alcohol	4.0
- polyethylene glycol monostearate	1.4
- glyceryl monostearate	2.4
- paraben	0.2
- purified water	remainder

#### Protective cream 2

- Some ingredients of protective cream 1 were replaced by the ingredients indicated below:

- composition 5; 1.0 %, by composition 13 or 22; 1.0 %;
- bleached beeswax; 1.0 %, by beeswax; 1.0 %; and,
- paraben; 0.2 %, by pigment; 0.003 % and glyceryl tri-(2-ethylhexanoate; 0.06 %.

45

### PREPARATION OF LOTION

To prepare the lotion, the method described for the cream was applied mutatis mutandis.

#### Lotion 1

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Ingredients, % by weight:	
- composition 2, 6 or 17	1.5
- glycerine	2.0

## EP 0 875 232 A1

(continued)

Ingredients, % by weight:	
- 1, 3-butylene glycol	2. 0
- sodium citrate	0. 1
- citric acid	0. 1
- ethanol	5. 0
- polyethylene oleyl ether	0. 5
- purified water	remainder

### Lotion 2

1. 5 % by weight of composition 2, 6 or 17 of lotion 1 were replaced by 0. 4 % by weight of composition 14 or 23.

### PREPARATION OF MILKY LOTION

A water phase and an oily phase were prepared at 70 °C as mentioned for the preparation of cream. Both phases were cooled to a temperature between 40 and 50 °C, combined, homogenized and emulsified. The resultant solution was cooled to 30 °C under stirring, to obtain a milky lotion.

#### Milky lotion 1

Ingredients, % by weight:	
- composition 3, 7 or 19	1. 5
- liquid paraffin	5. 0
- bleached beeswax	2. 0
- cetyl alcohol	0. 5
- stearic acid	1. 5
- glyceryl monooleate	1. 0
- glyceryl monostearate	2. 4
- polypropylene glycol	5. 0
- paraben	0. 3
- perfume	0. 05
- purified water	remainder

#### Milky lotion 2

Some ingredients of the milky lotion 1 were replaced by the ingredients indicated below.

- composition 3, 7 or 19; 1. 5 %, by composition 15 or 24; 0. 9 %.
- bleached beeswax; 2. 0 %, by beeswax; 2. 0 %; and
- paraben; 0. 3 %, by methylparaben; 0. 1 % and ethylparaben; 0. 3 %.

### PREPARATION OF SHAMPOO

To prepare the shampoo, the method described for the milky lotion was applied mutatis mutandis.

Shampoo 1

5	Ingredients, % by weight:	
	- composition 4, 8 or 18	1.5
	- triethylamine lauryl sulphate	18.5
10	- 1 % aqueous solution of hydroxypropylmethyl cellulose	15.0
	- ammonium lauryl sulphate	8.0
	- 1, 3-dimethylol-5, 5-dimethyl hydantoin	0.15
	- disodium ethylenediamine tetraacetate	0.05
15	- citric acid	trace
	- sodium chloride	trace
	- perfume	0.85
20	- purified water	remainder

Shampoo 2

The composition of shampoo 1 was replaced by the composition as indicated below:

- 25
- composition 4, 8 or 18; 1.5 %, by composition 13 or 22; 0.4 %.

In addition, following ingredients were added:

30	- decanoic acid	0.05 %
	- cocamide	4.0 %
35	- palmitic acid	0.3 %
	- glyceryl tri-(2-ethylhexanoate)	0.02 %

PREPARATION OF HAIR-TREATMENT LOTION

40 To prepare the hair-treatment lotion, the method described for the milky lotion was mutatis mutandis applied.

Hair-treatment lotion 1

45	Ingredients, % by weight:	
	- composition 1, 10 or 18	1.5
50	- hydroxyethyl cellulose	0.4
	- ethanol	25.0
	- glyceryl monooleate	2.0
	- paraben	0.2
55	- perfume	0.1
	- purified water	remainder



## Hair-treatment lotion 2

1. 5 % by weight of composition 1, 10 or 18 of hair-treatment lotion 1 were replaced by 0. 9 % by weight of composition 14 or 23.

## PREPARATION OF LIPSTICK

To prepare the lipstick, the method mentioned for the milky lotion and known manufacturing method were applied mutatis mutandis.

## Lipstick 1

Ingredients, % by weight:	
- composition 5	0. 5
- liquid lanoline	18. 0
- paraffin	15. 0
- titanium mica	10. 0
- glyceryl tri-(caprate, caprylate)	12. 0
- paraben	0. 1
- organic pigment	8. 0
- castor oil	remainder

## Lipstick 2

Some ingredients of lipstick 1 were replaced by the ingredients as indicated below:

- composition 5; 0. 5 %, by composition 13 or 22; 0. 5 %;
- glyceryl tri-(caprylate, caprate); 12. 0 %, by glyceryl tricaprato; 6. 0 % and glyceryl tricaprato; 6. 0 %;
- castor oil; remainder, by ricin oil; remainder.

## EVALUATION BY USERS 1

The products described below were prepared with and without (blank) the composition according to the invention and tested by 20 panellists. As for cream, lotion and milky lotion, the products were applied on the skin of their upper arm. The panellists then compared the products and the corresponding blank samples on the spreadability, affinity and moist and tender feeling to the skin. As for shampoo and hair-treatment lotion, hair-wiriness and wet tenderness after hair washing were compared between the products and the blank samples. Results of evaluation are shown by the number of panellists consisting of 20 persons who responded positively on the product over the blank sample.

Type of product	Evaluation
- cream (composition 1)	19 / 20
- lotion (composition 2)	18 / 20
- milky lotion (composition 3)	18 / 20
- shampoo (composition 4)	17 / 20
- hair-treatment lotion (composition 1)	18 / 20

## EVALUATION BY USERS 2

The products described below were prepared with and without (blank) the composition according to the invention and tested by panellist group A consisting of 20 female monitors aged 23 to 35, having healthy skin, and by panellist group B consisting of 20 female monitors aged 33 to 48, perceiving dry, damaged or wrinkled skin. Test was carried out in relatively dry season covering November to December. To test cream, protective cream, lotion, milky lotion and lipstick, monitors previously took a bath and washed the face. Then, without using other cosmetics, the products according to the invention were applied on the right-half of the face and the inside portion of the right upper arm, whilst the blank products on the left-half of the face and the inside portion of the left upper arm. The products and blank products were applied once to three times a day for 20 consecutive days.

To test shampoo and hair-treatment lotion, monitors previously washed hair with soap. Then, without using other hair-cosmetics, the products according to the invention were applied on the right-half of the scalp, whilst the blank products on the left-half of the scalp. The products and blank products were applied once or twice a day for 20 consecutive days. Evaluation criteria were the same as those for "Evaluation by users 1".

Type of product	EVALUATION	
	Group A	Group B
- cream (composition 5)	15 / 20	18 / 20
- protective cream (composition 5)	16 / 20	17 / 20
- lotion (composition 6)	17 / 20	16 / 20
- milky lotion (composition 7)	14 / 20	17 / 20
- shampoo (composition 8)	14 / 20	16 / 20
- hair-treatment lotion (composition 10)	17 / 20	18 / 20
- lipstick (composition 1)	13 / 20	15 / 20

## EVALUATION BY USERS 3

In "Evaluation by users 2", the compositions 5, 5, 6, 7, 8, 10 and 1 were replaced, in the corresponding order, by compositions 13, 13, 14, 15, 13, 14 and 13, so that the corresponding types of product were obtained. The products were then tested for evaluation, in the same way as described in "Evaluation by users 2".

The results of evaluation obtained were substantially the same as those of "Evaluation by users 2".

## EVALUATION BY USERS 4

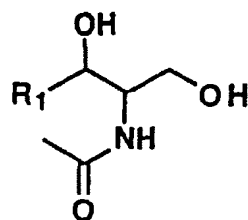
In "Evaluation by users 2", the compositions 5, 5, 6, 7, 8, 10 and 1 were replaced, in the corresponding order, by compositions 22, 22, 23, 24, 22, 23 and 22, so that the corresponding types of product were obtained. The products were then tested for evaluation, in the same way as described in "Evaluation by users 2".

The results of evaluation obtained were substantially the same as those of "Evaluation by users 2".

## Claims

## 1. A composition comprising :

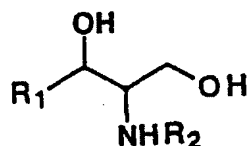
- at least a component A chosen from the group consisting of 2-acetaminoalkane-1,3-diols having the formula (I):



(I)

in which R1 signifies a linear alkyl group having 9 to 17 carbon atoms; and an optically active substance thereof;

- at least a component B chosen from the group consisting of 2-acylaminoalkane-1,3-diols having the formula (II):



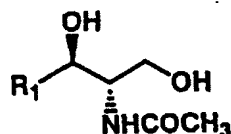
(II)

in which R1 has the same meaning as mentioned above and R2 signifies a linear acyl group having 14 to 24 carbon atoms; a derivative thereof where at least one of said carbon atoms in the acyl group has a substituting group, and /or a double bond;

- and an optically active substance of either of said diol or derivative; and
- at least a component C consisting of sterol group,

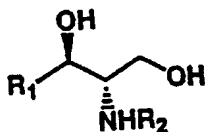
said components A, B and C being mixed in such a proportion as to form a liquid crystal phase.

- The composition according to claim 1, wherein said sterol is cholesterol.
- The composition according to claims 1 or 2, wherein said components A and B are mixed in a weight proportion ranging from 1 : 1 to 1 : 8.
- The composition according to any one of claims 1 to 3, wherein said component A is a (2S, 3R)-2-acetaminoalkane-1, 3-diol having formula (III):



(III)

- The composition according to any one of claim 1 to 4, wherein said component B is a (2S, 3R)-2-acylaminoalkane-1, 3-diol having formula (IV):



(IV)

6. The composition according to any one of claims 1 to 5, wherein said R<sub>2</sub> in the component B is an acyl group having a hydroxy group on the position of carbon-2.
7. The composition according to any one of claim 1 to 6, wherein said R<sub>2</sub> in the component B is oleoyl group.
8. The composition according to claim 7, wherein the weight proportion of said components A to B, said components B to C and said components A to C ranges from 1 : 1 to 1 : 8, from 7 : 1 to 1 : 1 and from 1 : 1 to 1 : 3 respectively.
9. The composition according to any one of claims 1 to 7, which further comprises at least a component D chosen from the group consisting of a derivative of cholesterol, a fatty acid and a derivative thereof.
10. The composition according to claim 9, wherein said derivative of cholesterol as component D is cholesteryl hydroxystearate.
11. The composition according to claim 10, wherein the total of said components A and B, and said cholesterol as component C are mixed so as to give a weight proportion of (A + B) to C ranging from 5 : 4 to 5 : 1 and said cholesterol as component C and said cholesteryl hydroxystearate as component D are mixed so as to give a weight proportion of C to D ranging from 4 : 1 to 1 : 5.
12. The composition according to claim 9, wherein said fatty acid as component D is isostearic acid.
13. The composition according to claim 9, wherein said derivative of a fatty acid as component D is cholesteryl hydroxystearate.
14. The composition according to claim 12, wherein the total of said components A and B, and said cholesterol as component C are mixed so as to give a weight proportion of (A + B) to C ranging from 5 : 1 to 3 : 1 and said cholesterol as component C and said isostearic acid as component D are mixed so as to give a weight proportion of C to D ranging from 1 : 1 to 1 : 4.
15. The composition according to any one of claims 1 to 14, which further comprises at least one compound chosen from the group consisting of a triglyceride and a phospholipid.
16. A cosmetic product comprising the composition defined in any one of claims 1 to 15, which further comprises a cosmetically allowable medium.
17. Use of the cosmetic product according to claim 16, as a skin-protecting agent.
18. Use of the cosmetic product according to claim 16, as an agent to be added in baths.
19. Use of the cosmetic product according to claim 16, as a hair-protecting agent.
20. A pharmaceutical product comprising the composition defined in any one of claims 1 to 15, which further comprises a pharmaceutically allowable medium.
21. Use of the composition according to any one of claims 1 to 15 in the manufacture of a medicine for protecting skin.

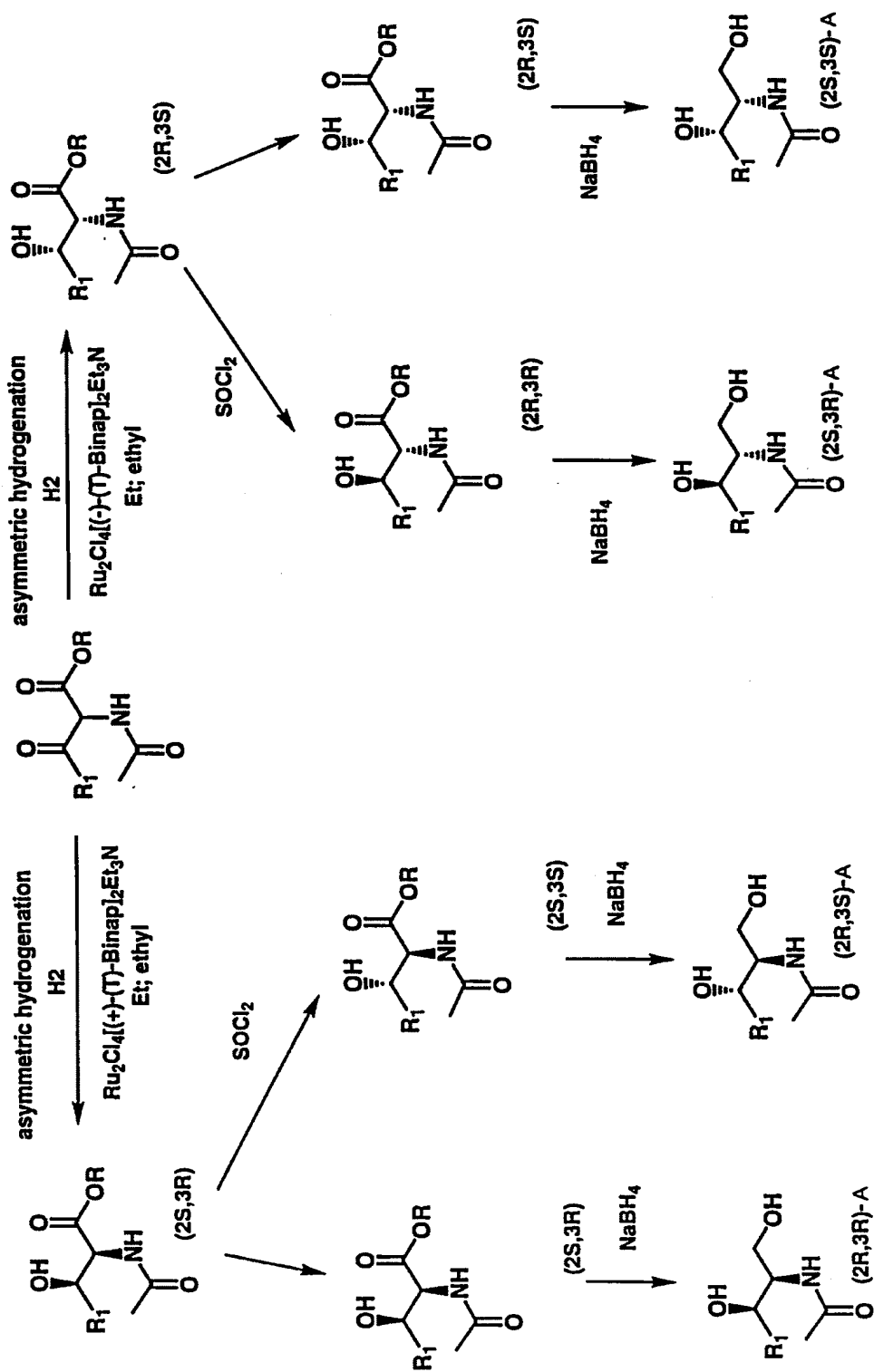


Fig. 1

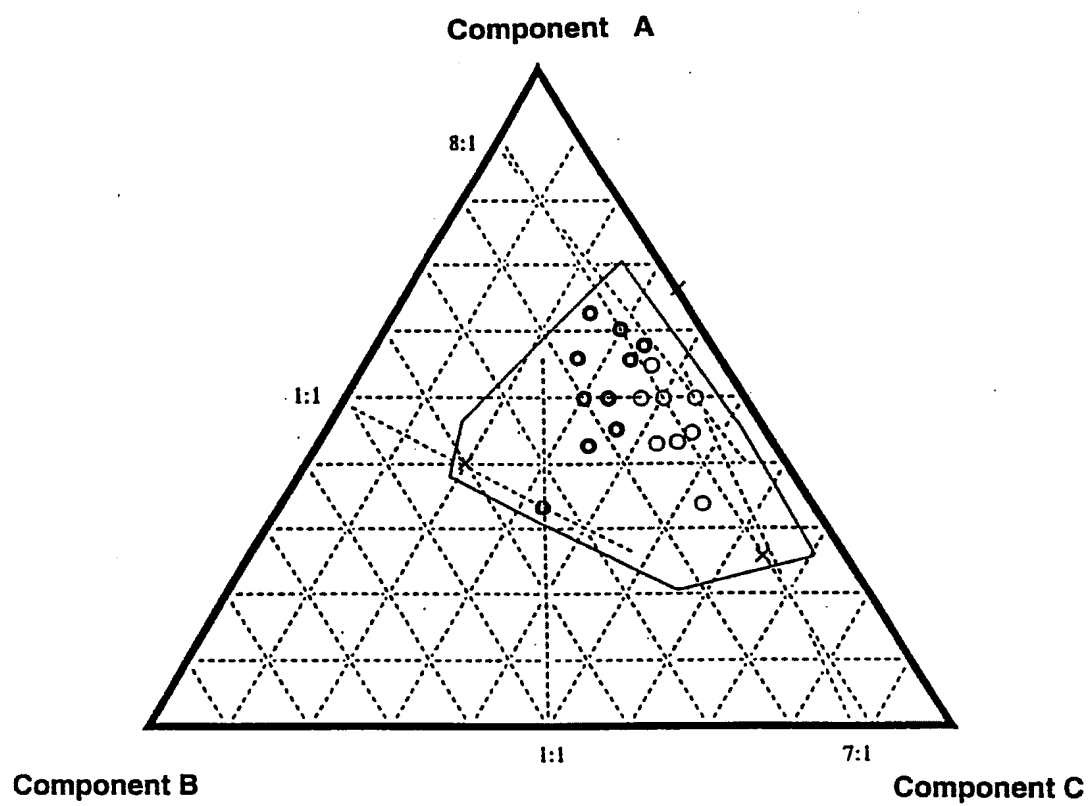
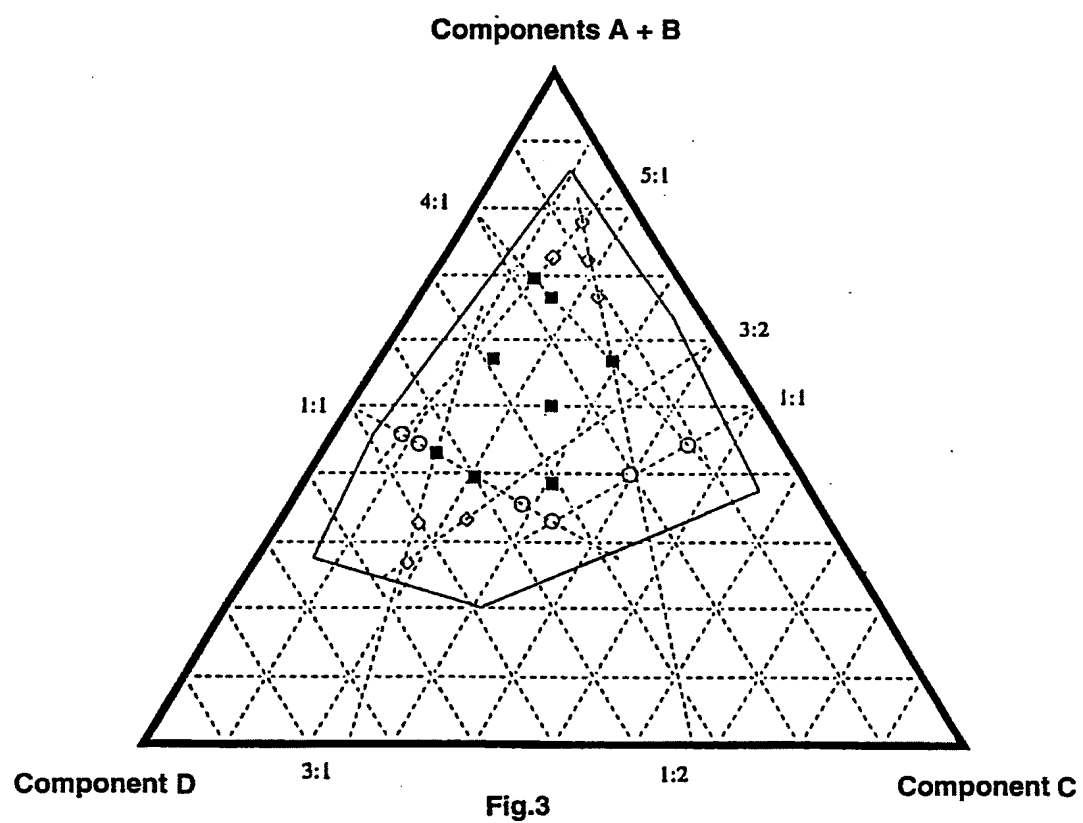
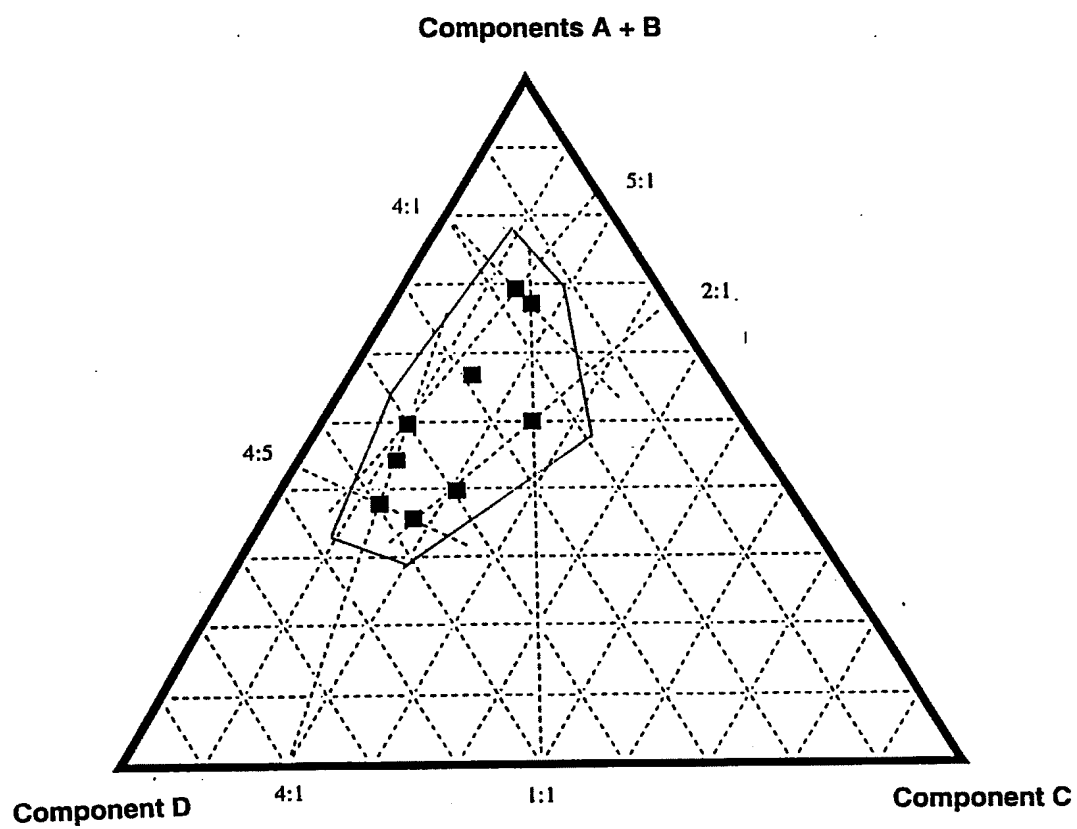


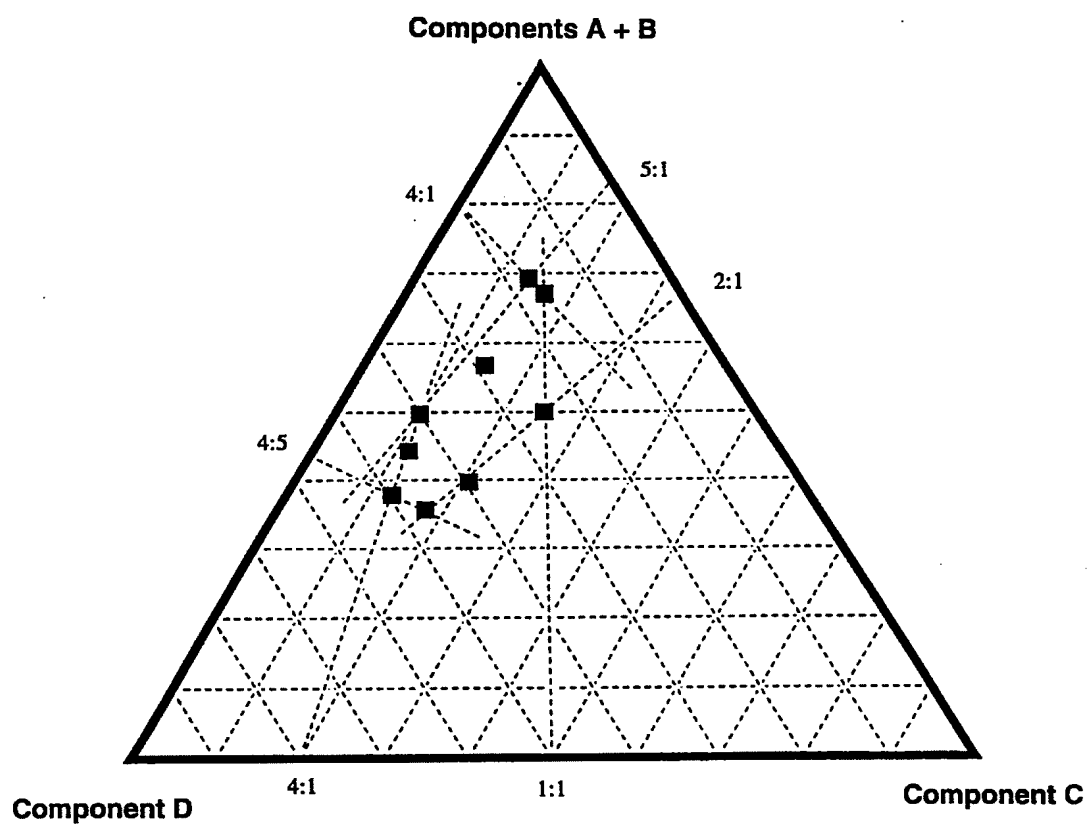
Fig.2



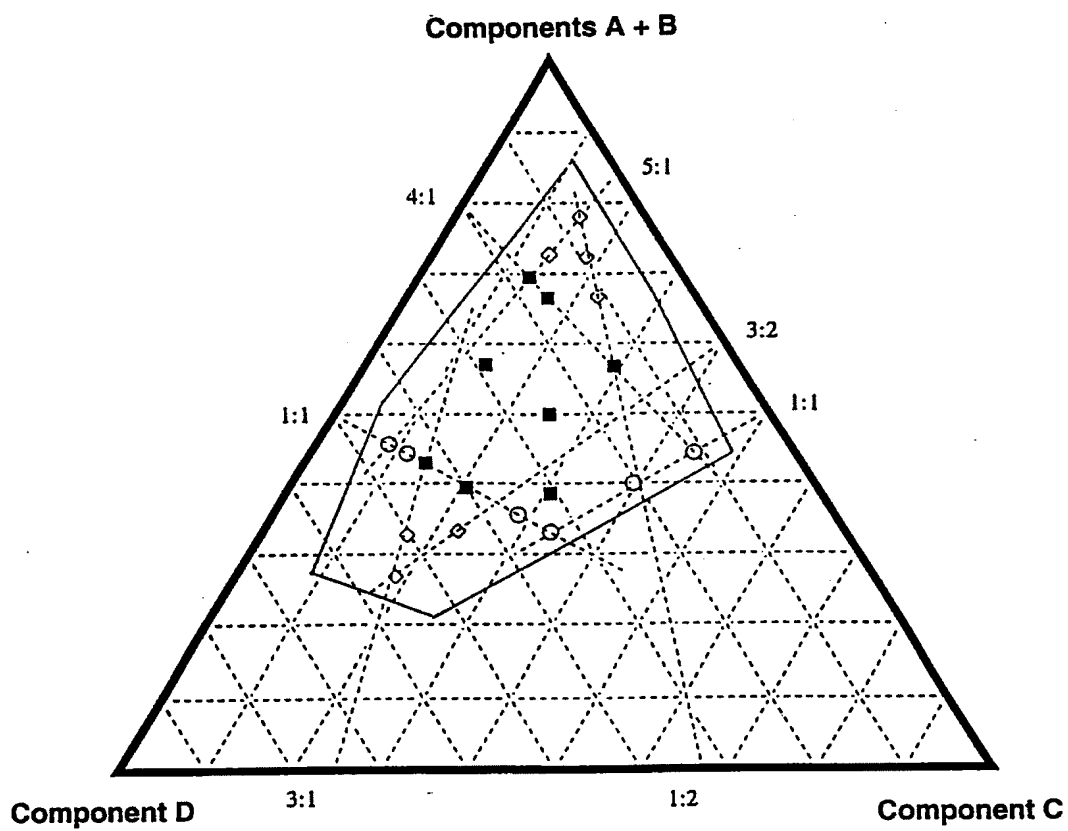


**Fig.4**





**Fig.5**



**Fig.6 .**

# Water Retention Test

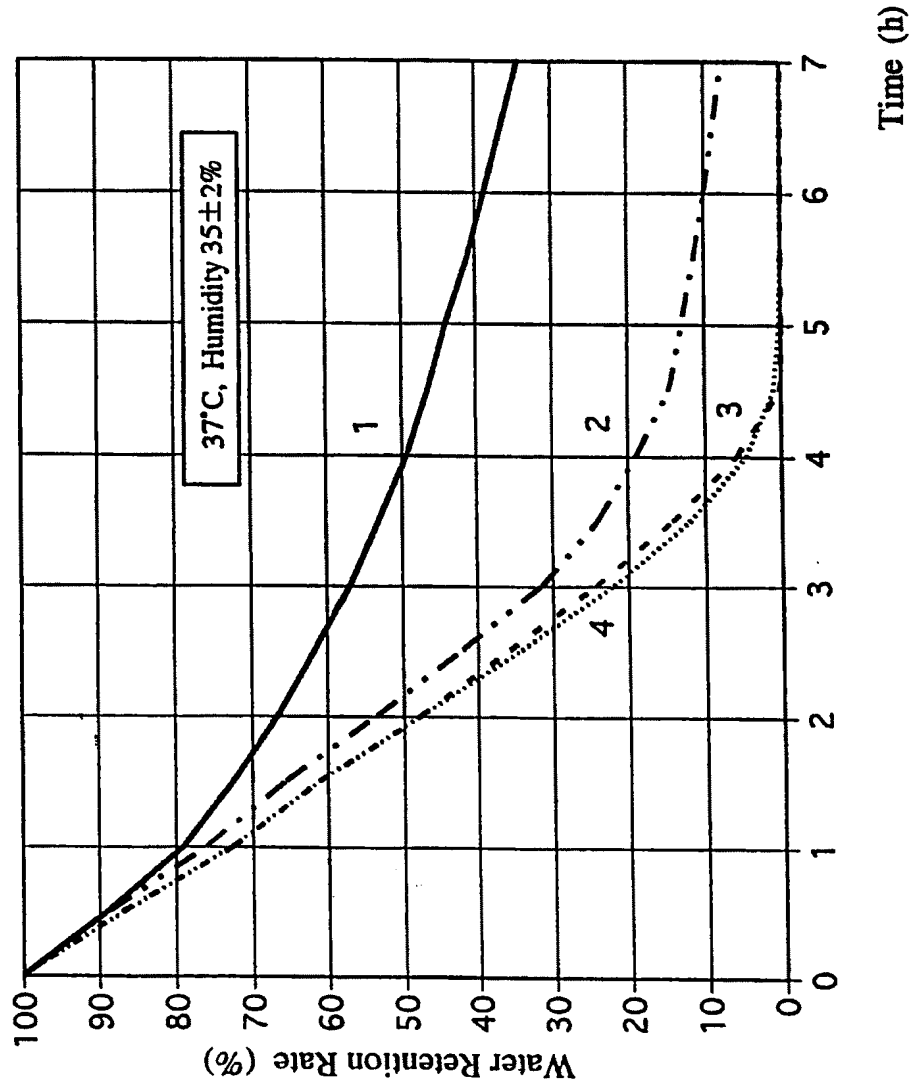


Fig.7

# Water Retention Test of Ceramide

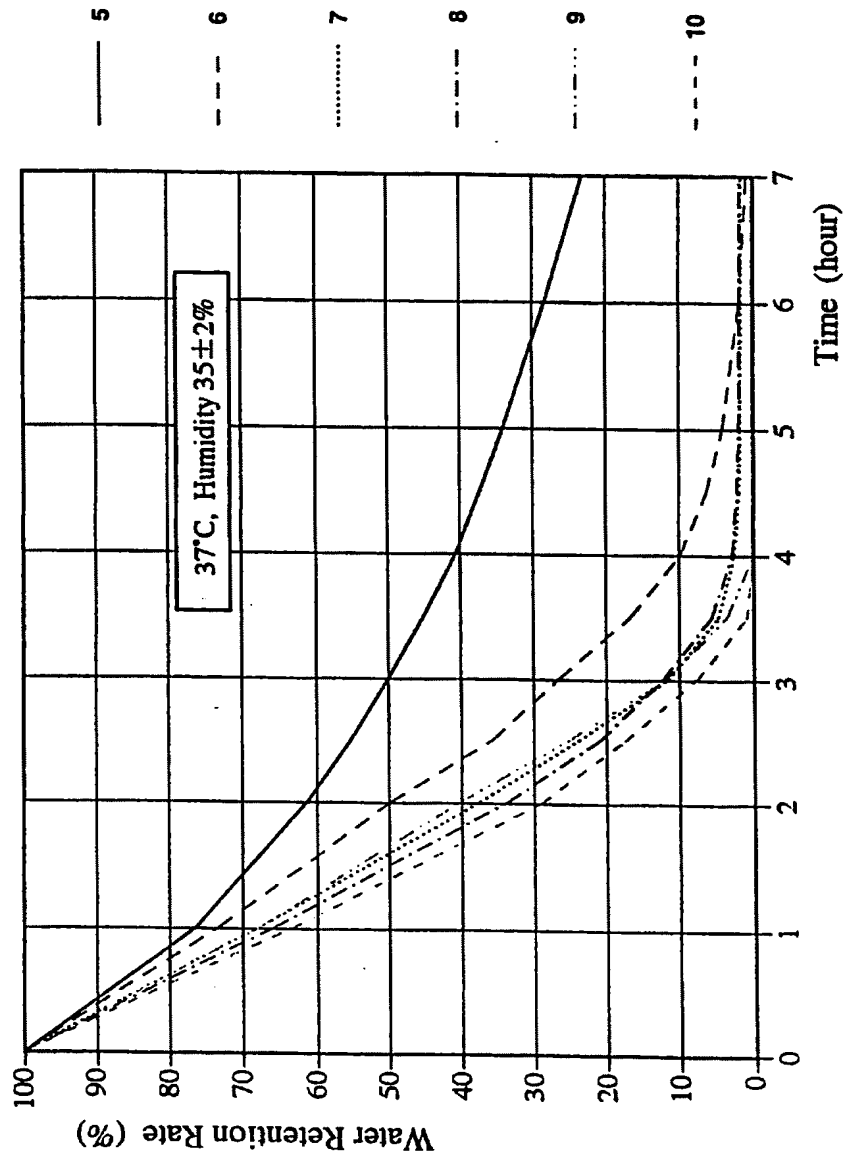


Fig.8

Water Retention Test

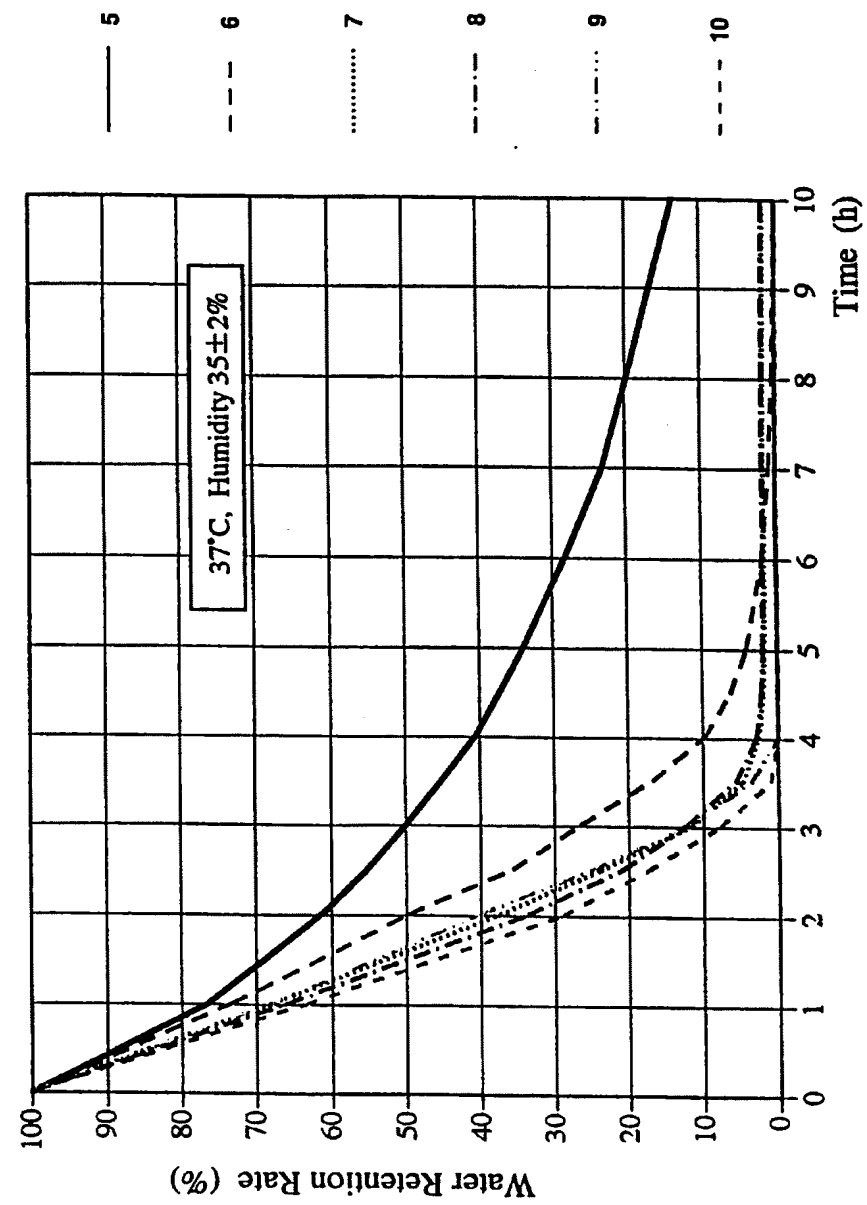
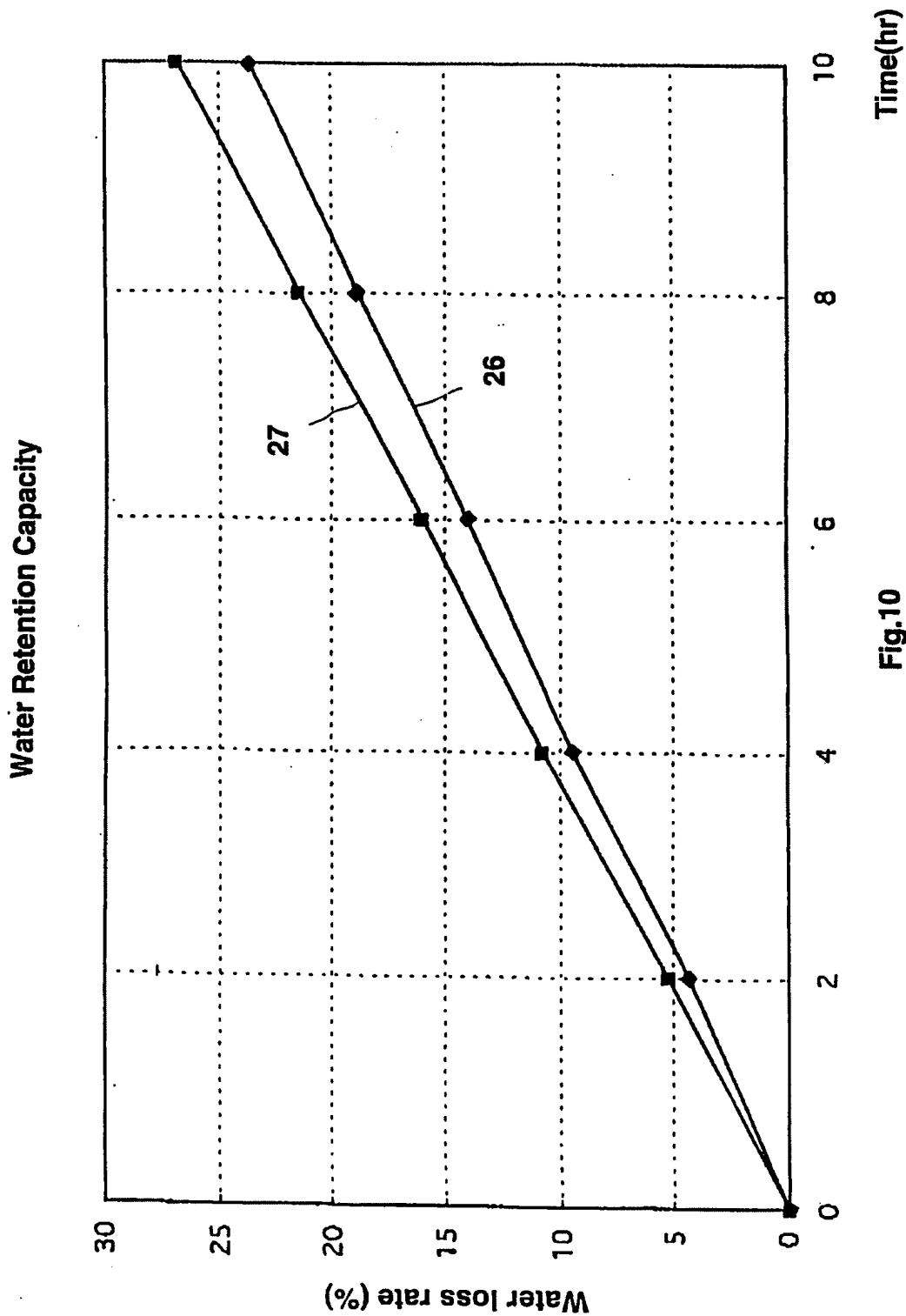


Fig.9



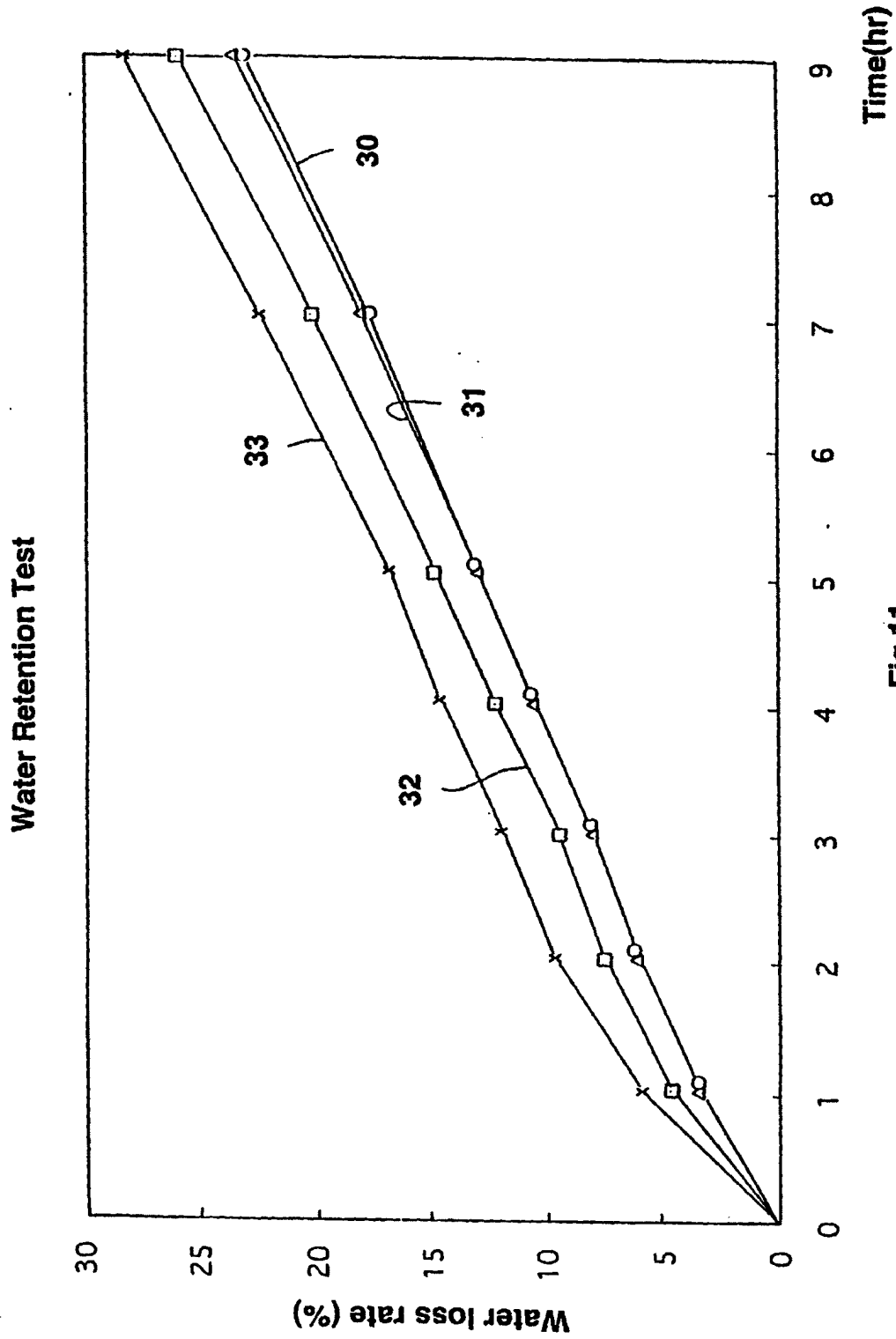


Fig.11

# Water Retention Test

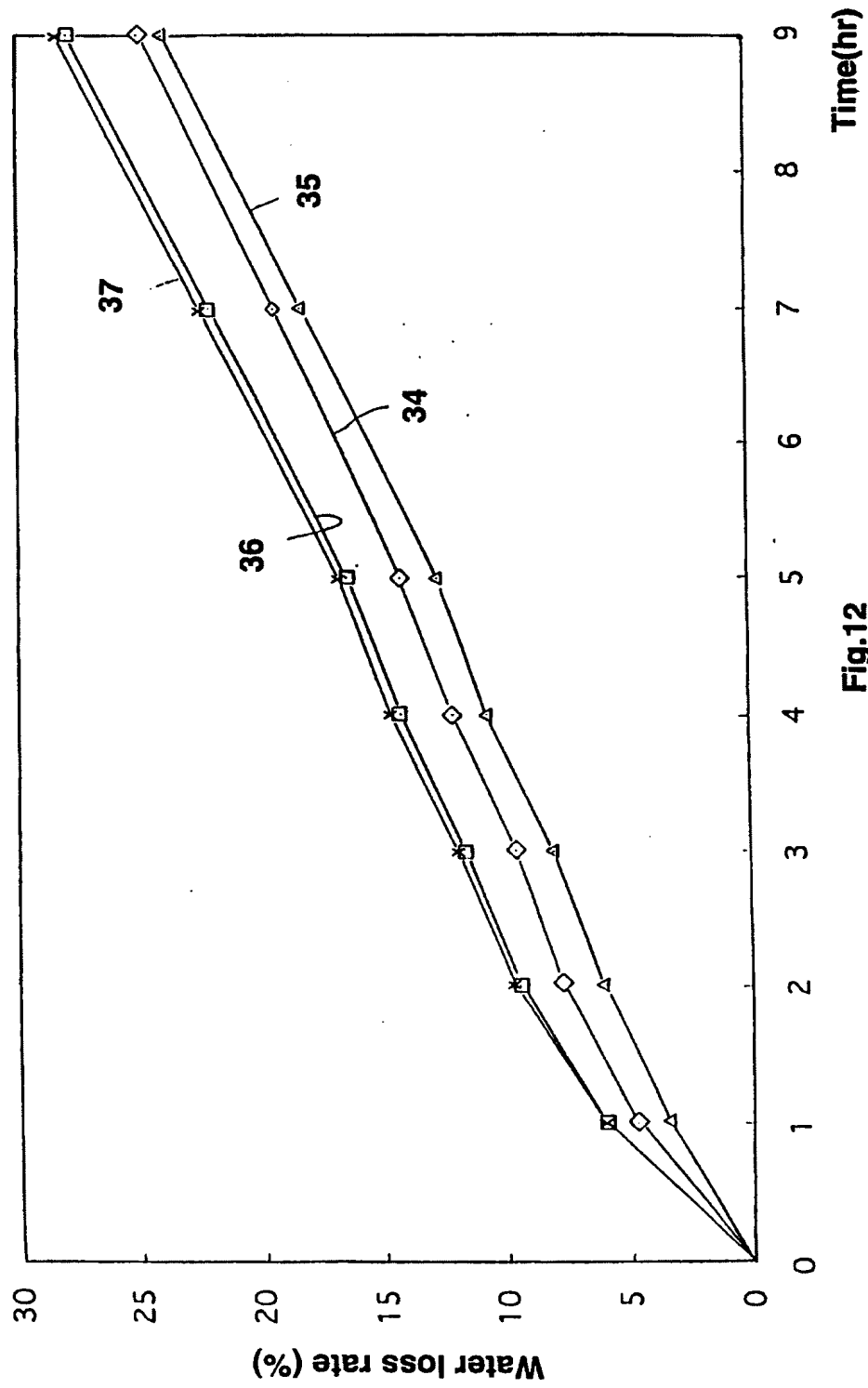


Fig.12





European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 97 40 0997

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	WO 93 00068 A (L'OREAL) 7 January 1993 * claims 29,30; example 4 * ---	1	A61K7/00 A61K7/48
A	EP 0 554 897 A (KAO) 11 August 1993 * page 3, line 4 - page 4, line 5; claim 13 * ---	1	
A	DATABASE WPI Week 9312 Derwent Publications Ltd., London, GB; AN 93-096928 XP002042505 "Liq. crystal compsn. for toiletries etc. - contains phospho, glyco- and /or sphingolipid(s), sterol, and one or more of electrolyte, polysaccharide drug extract and low molecular cpd." & JP 05 039 485 A (KOSE) , 19 February 1993 * abstract * ---	1	
A	DATABASE WPI Week 9510 Derwent Publications Ltd., London, GB; AN 95-70205 XP002042506 "Highly stable skin care agent - contains amphipathic lipid(s), nonionic and ionic surfactants, oil agent(s) and aq. media" & JP 06 345 633 A (KAO) , 20 December 1994 * abstract * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
D,A	EP 0 278 505 A (ESTEE LAUDER) 17 August 1988 * claim 1 * -----	1	
The present search report has been drawn up for all claims			
Place of search <b>THE HAGUE</b>		Date of completion of the search <b>3 October 1997</b>	Examiner <b>Voyiazoglou, D</b>
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

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